STUDY ON INCIDENCE OF CONTRAST INDUCED NEPHROPATHY IN PATIENTS UNDERGOING CONTRAST USING PROCEDURE- CORONARY ANGIOGRAM WITH NORMAL RENAL FUNCTION

Submitted in partial fulfillment of requirements of

M.D. DEGREE BRANCH - I
GENERAL MEDICINE
of
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Dr.M.G.R. MEDICAL UNIVERSITY,
CHENNAI.

STANLEY MEDICAL COLLEGE AND HOSPITAL
CHENNAI-600001

APRIL 2014

DECLARATION

I solemnly declare that this dissertation entitled "**STUDY ON INCIDENCE OF CONTRAST INDUCED NEPHROPATHY IN PATIENTS UNDERGOING CONTRAST USING PROCEDURE -CORONARY ARTERY ANGIOGRAM WITH NORMAL RENAL FUNCTION**" is done by me at Government Stanley medical college and Hospital during 2011-2014 under the guidance and supervision of Prof.Vijayaraghavan, M.D. This dissertation is submitted to Tamil Nadu Dr.M.G.R. Medical University, towards the partial fulfillment of requirement for the award of M.D. Degree General Medicine (Branch - I).

Place:

Date Dr.S.Vanitha

CERTIFICATE

This is to certify that this dissertation entitled " **TO STUDY THE INCIDENCE OF CONTRAST INDUCED NEPHROPATHY IN PATIENTS UNDERGOING CONTRAST IMAGING STUDY-CORONARY ARTERY ANGIOGRAM WITH NORMAL RENAL FUNCTION**" submitted by Dr.S.Vanitha appearing for M.D. Branch I General Medicine Degree examination in April 2014 is a bonafide record of work done by her under my direct guidance and supervision in partial fulfillment of regulations of the Tamil nadu Dr.M.G.R.Medical University Chennai, I forward this to the Tamilnadu Dr.M.G.R.Medical University, Chennai, Tamilnadu, India.

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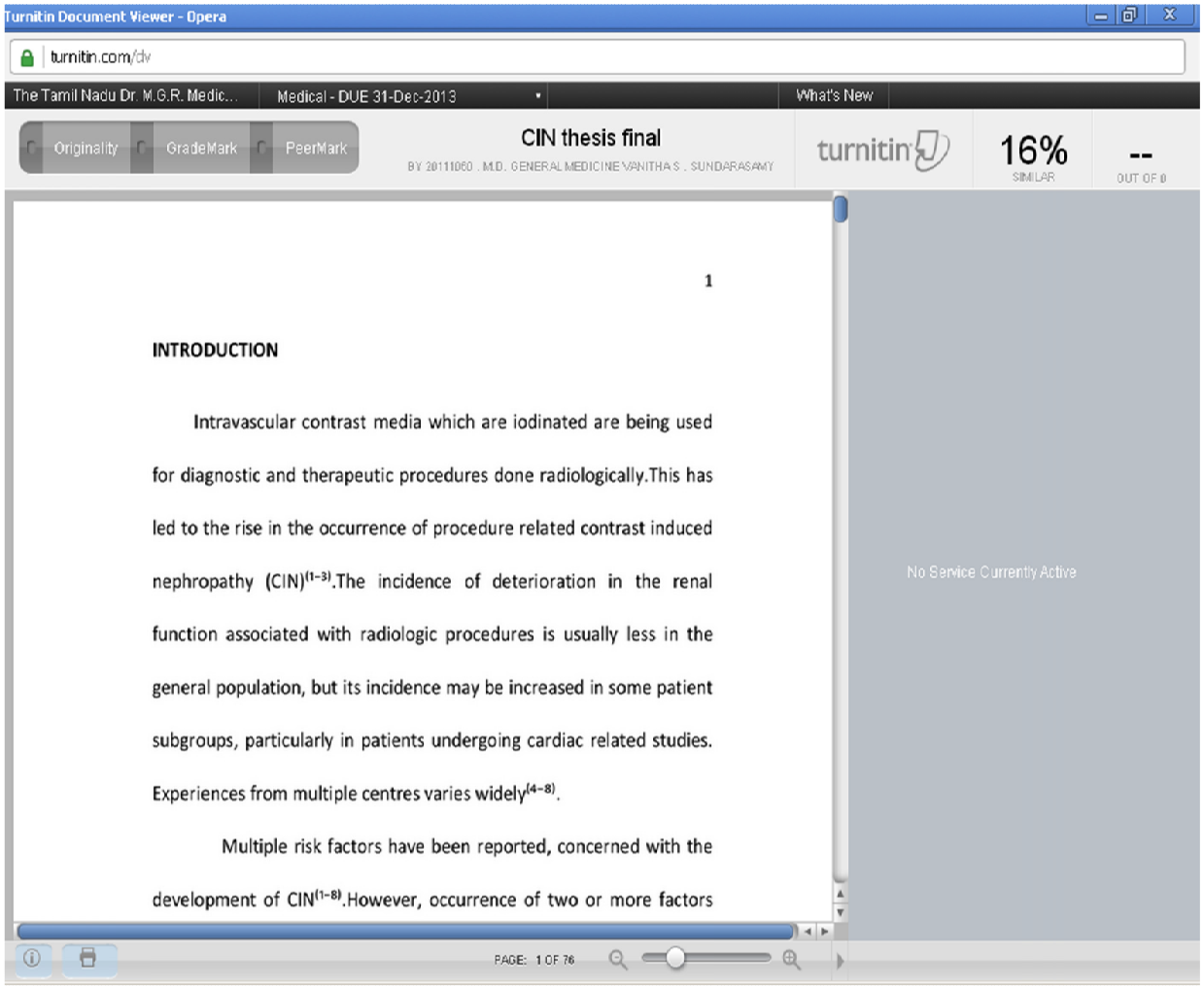
CONTENT

ABBREVIATIONS

CIN	-	Contrast induced nephropathy
PCI	-	Percutaneous coronary intervention
ACE I	-	Angiotensin converting enzyme inhibitors
CM	-	Contrast medium
HOCM	-	High osmolar contrast medium
LOCM	-	Low osmolar contrast medium
RBF	-	Renal blood flow
GFR	-	Glomerular filtration rate
ANP	-	Atrial natriuretic peptide
PG	-	Prostaglandin
NSAID	-	Non steroidal anti-inflammatory drugs
HT	-	Hypertension
DM	-	Diabetes mellitus.
NGAL	-	neutrophil gelatinase associated lipocalcin
NAC	-	N acetyl cysteine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INTRODUCTION
Intravascular contrast media which are iodinated are being used for diagnostic and therapeutic procedures done radiologically.This has led to the rise in the occurrence of procedure related contrast induced nephropathy (CIN)[1-3].The incidence of deterioration in the renal function associated with radiologic procedures is usually less in the general population, but its incidence may be increased in some patient subgroups, particularly in patients undergoing cardiac related studies. Experiences from multiple centres varies widely[4-8].
Multiple risk factors have been reported, concerned with the development of CIN[1-8].However, occurrence of two or more factors
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STUDY ON INCIDENCE OF CONTRAST INDUCED NEPHROPATHY IN PATIENTS UNDERGOING CONTRAST USING PROCEDURE-CORONARY ANGIOGRAM WITH NORMAL RENAL FUNCTION

Abstract

Iodinated contrast media used for radiological diagnostic and therapeutic procedures are associated with the incidence of contrast induced nephropathy, which is the third leading cause of acute kidney injury next to ischeamic renal injury and nehrotoxic medications.It also increases the in hospital mortality of the patients.The incidence is particularly more in patients subgroup who are undergoing cardiac related procedures.

The incidence of CIN is associated with multiple risk factors ,and we have studied some of such risk factors namely,age and gender of the patients, hypertension and diabetic status of the patient,smoking history, intake of nephrotoxic drugs like ACE inhibitors, NSAIDS, Nephrotoxic antibiotics, Diuretics and the hydration and anemic status of the patients, who are undergoing coronary angiogram, a contrast using procedure having normal renal function, over a period of three months, in our hospital.Out of the risk factors studied, the most contributing risk factor is diabetic status of the patient , according to our study.The inclusion of only small number of patients, the inclusion of only some of the risk factors involved ,and absence of use of any prophylactic measures either pharmacological or non pharmacological for the prevention of contrast induced nephropathy are some of the limitations in our study.Also there is need for long term followup of the patient to study for the incidence of chronic kidney disease.

Key words: Contrast induced nephropathy, Risk factors, Coronary angiogram, Iodinated contrast media

INTRODUCTION

Intravascular contrast media which are iodinated are being used for diagnostic and therapeutic procedures done radiologically.This has led to the rise in the occurrence of procedure related contrast induced nephropathy (CIN)[1–3].The incidence of deterioration in the renal function associated with radiologic procedures is usually less in the general population, but its incidence may be increased in some patient subgroups, particularly in patients undergoing cardiac related studies. Experiences from multiple centres varies widely[4–8].

Multiple risk factors have been reported, concerned with the development of CIN[1–8].However, occurrence of two or more factors together is rather common in day to day practice, and their additive effect on renal function is not well studied. This urges the necessity for wide assessment of the effect of these variable risk factors on the development of CIN.

CIN is the third leading cause of hospital acquired acute kidney injury (next to decreased renal perfusion and nephrotoxic medications)[9].In hospital mortality rate of CIN is as high as 14%[11].In patients with multiple risk factors, incidence of CIN can rise upto 50% or even greater[12].

CIN increases the length of stay in the hospital, need for extra medical care, and also the mortality[13].This study aims to study the incidence of contrast induced nephropathy in contrast using procedure – coronary angiogram, in patients who have no abnormal renal function.

AIM OF THE STUDY

To study the incidence of contrast induced nephropathy in patients undergoing contrast using procedure- coronary angiogram, with normal renal function .

Review of Literature

Contrast induced nephropathy is defined as a new onset or an exacerbation of existing renal dysfunction after contrast administration in the absence of other causes, with s.creatinine increase of ≥25% over the baseline value or an absolute increase of ≥0.5mg/dl[14–18]. S.creatinine starts rising within 24-48 hours after exposure ,with creatinine peaking at 5-7 days.It normalises usually within 7-10 days[19].CIN is the third most common hospital acquired renal failure.

PATHOGENESIS OF CIN

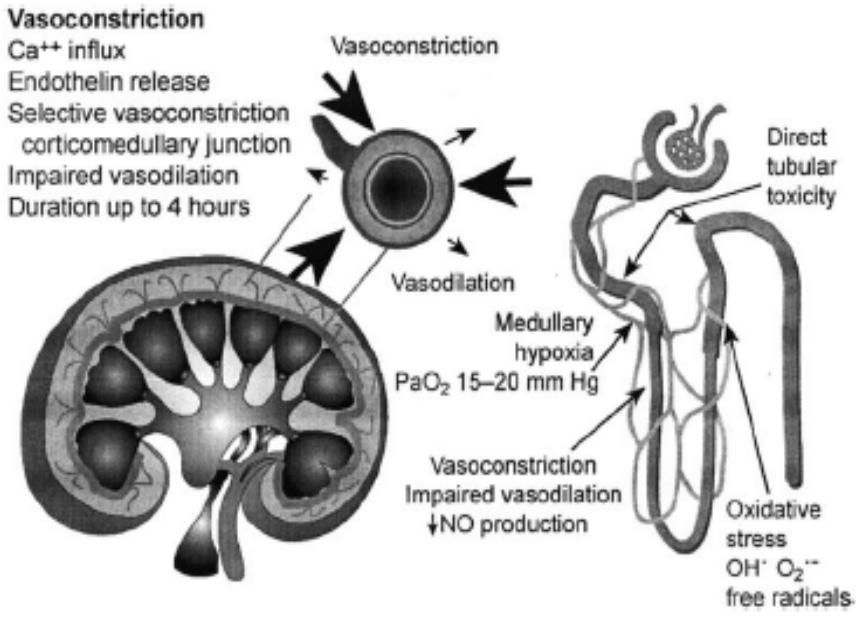
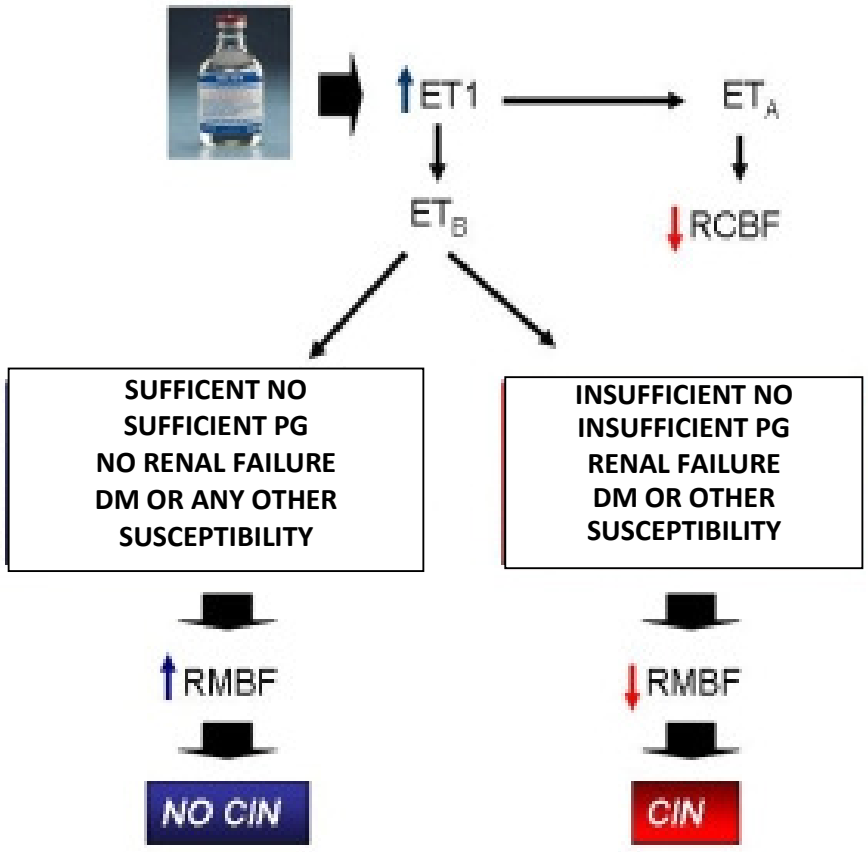


Figure 1 Overview of the factors involved in the pathogenesis of CIN NO=nitric oxide, OH^- = hydroxyl radical, O^-_2 Superoxide radical, PaO_2 = arterial oxygen pressure.

The pathogenesis of CIN is thought to be multifactorial and the exact mechanism is still not certain.It is said to be dependent on the free radicals produced in the renal medulla's acidic environment . The hyperosmolar stress while using certain contrast agents stimulate the production of reactive oxygen species leading to direct cytotoxicity and renal tubular and glomerular cells apoptosis[20–22].

Many animal studies have shown that there is constriction of the vasa recta related to contrast media seen in the outer medulla associated with a decline in the blood flow to the renal medulla, filtration rate in the glomeruli, velocity of the erythrocytes and the oxygen tension, with an incline in the aggregation of erythrocytes. There is also an elevated adenosine, endothelin and free radical induced constriction of blood vessels and decreased nitric oxide,prostaglandin induced dilatation of blood vessels leading to ischeamia in the inner portions of outer medulla, where high oxygen is needed. Immunological etiologies have been proved as well[30–32].

Figure 2 Proposed role of endothelin 1 in the development of CIN. (ET1: Endothelin 1, ETA: Endothelin A receptor, ETB: Endothelin B receptor, RCBF: renal cortical blood flow, RMBF: renal medullary blood flow, NO: nitric oxide, PG: prostaglandins, DM: diabetes mellitus, CIN: contrastinduced nephropathy



Increased endothelin B causing insufficient Nitric oxide, insufficient prostaglandin level leading to decreased renal medullary blood flow , finally leading to the incidence of CIN.

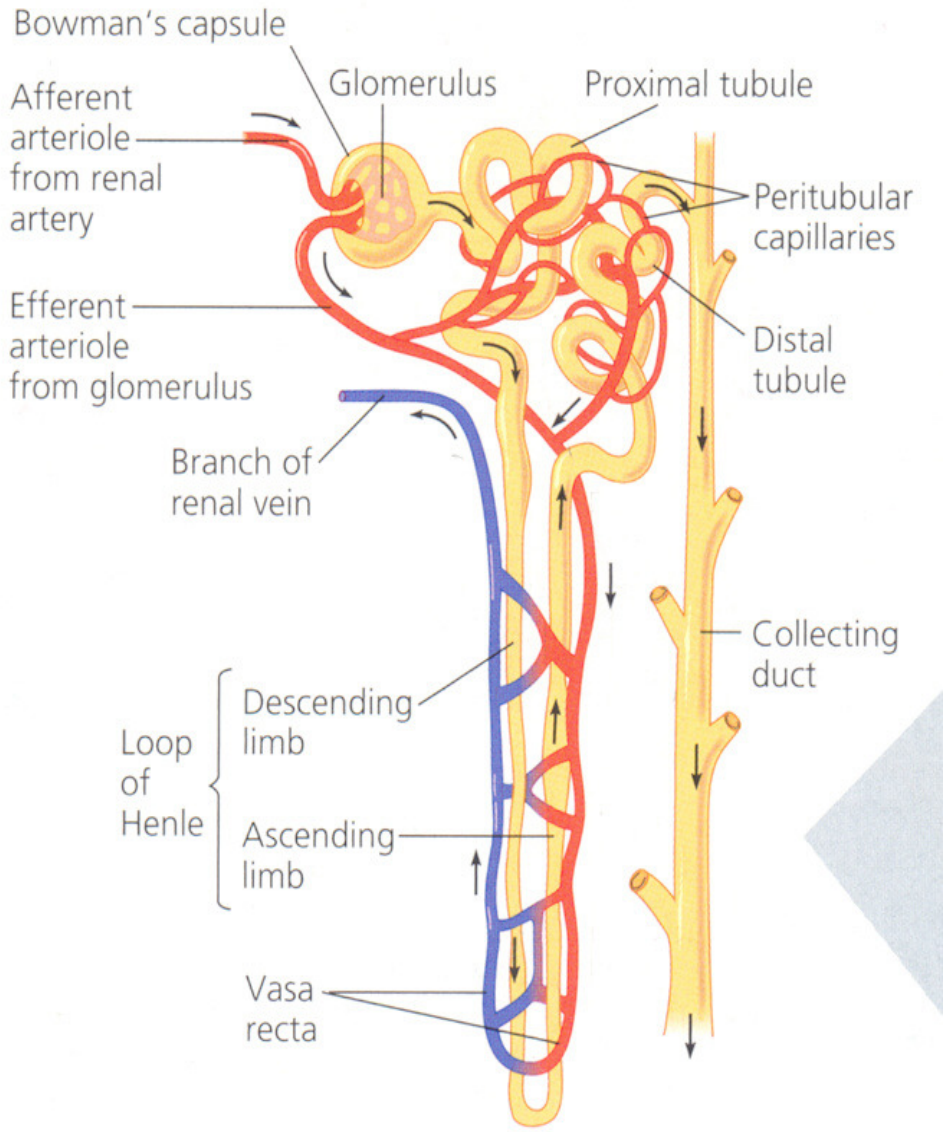


Figure 3 STRUCTURE OF GLOMERULUS

The structure of the glomerulus where the direct toxic effect on renal tubules and the vasocontrictive effect on renal vessels after the exposure to contrast media takes place.

Renal disease due to atheroembolism can also lead to worsening of renal function ,post contrast study.Hence it should also be considered as one of the cause for post contrast renal function deterioration[33].

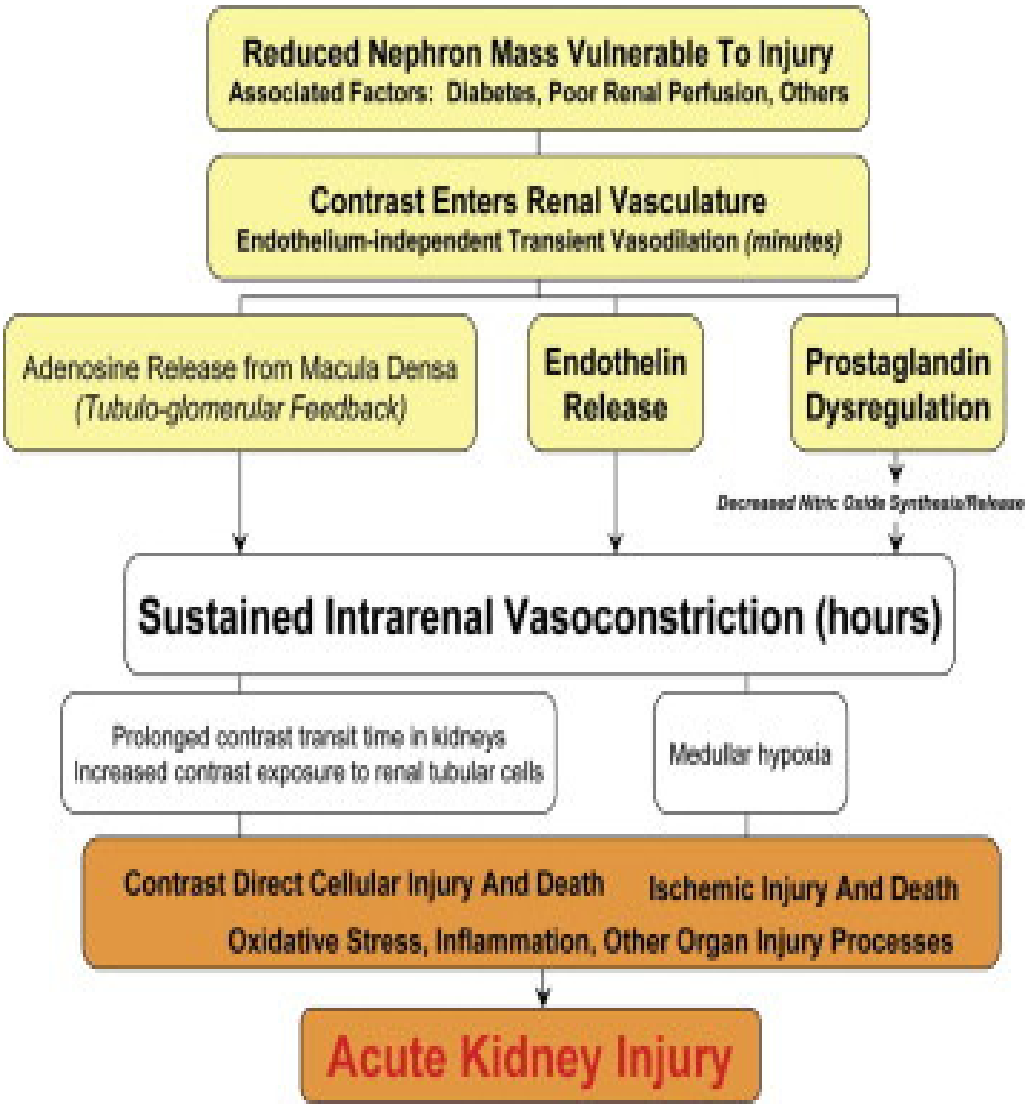
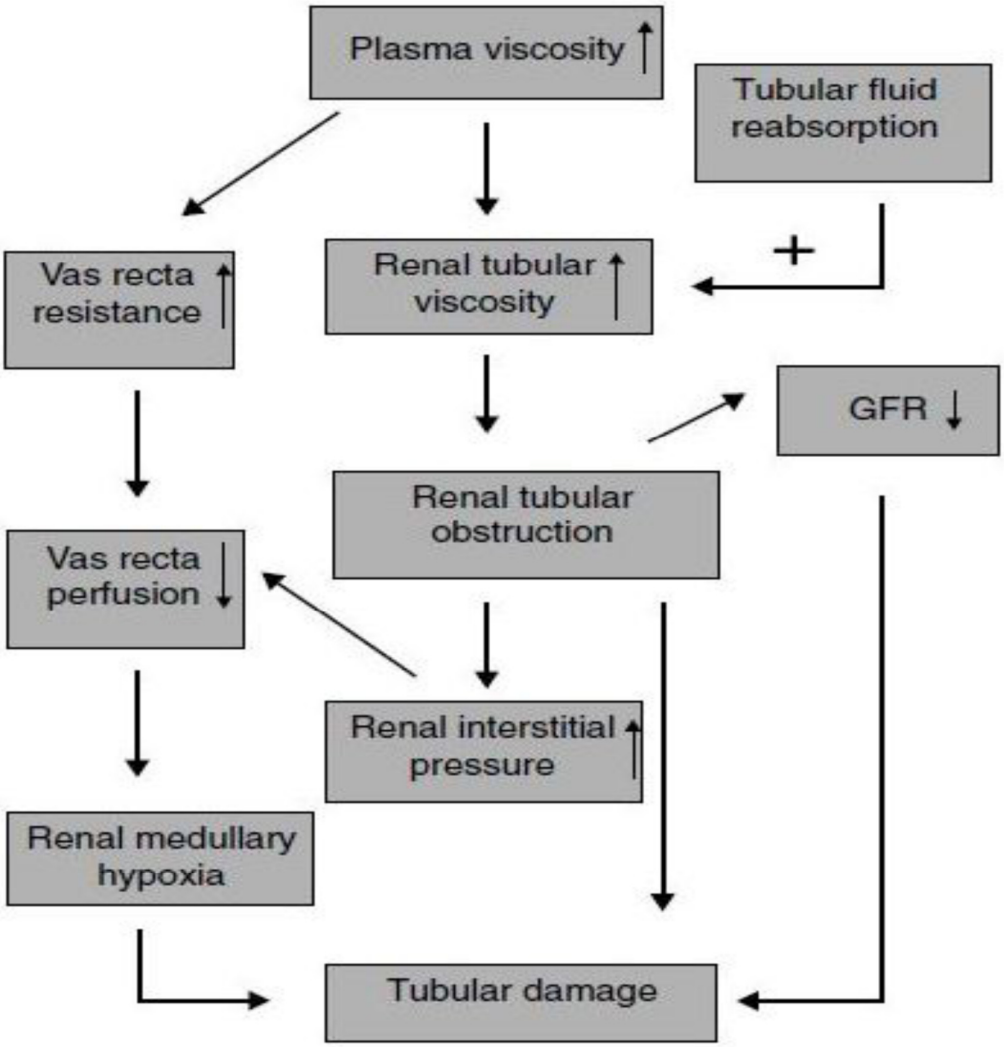


Figure 4 : Explaining the role of osmalality of the contrast media in the pathogenesis of CIN

The osmolality of the contrast media has been proved to have some role in the pathogenesis of CIN , as evidenced by many clinical and experimental studies[34].Contrast media given intravenously is shown to have lesser adverse effects than given intra-arterially. Also the amount needed is smaller with the intravenous route when compared to the other and also the osmolality of the media gets decreased in the circulation before it reaches the kidney [35].There is a relationship between osmolality and that of viscosity of the agent used.Contrast media having increased osmolality than that of plasma, increases the fluid viscosity, and thus elevating the resistance to the flow within the renal tubules[36].The viscosity in the tubular fluid is isotonic at an osmolality of 300 mOsm/L and it is lesser than the plasma viscosity[36,37].The agents which have a lower osmolality actually have an osmolality 2-3 times more than the osmolality of plasma[35].High osmolar agents decreases the red blood cells deformability , thus the stiffness of red blood cells is increased and thus the flow of red blood cells through the capillaries more difficult[35,36].Making the red blood cells more deformed, with dilatation of systemic vessels , constriction of intrarenal vessels , and direct toxic effects on renal tubules are all seen with contrast agents

having an osmolality more than the blood[34].Patients having diabetes associated with renal failure are at increased risk for CIN due to decrease in endogenous vasodilators such as nitric oxide and prostaglandins, leading to decrease in renal blood flow and GFR [34,38].



Flow chart of mechanisms linking fluid osmolarity to renal damage

GFR - glomerular filtration rate

PHYSIOCHEMICAL CHARACTERS OF CONTRAST AGENTS

Contrast media used are classified into high-osmolar, low – osmalar, and iso-osmalar contrast agents.The toxicity of contrast media are defined by their osmolality,viscosity and chemotoxicity. The most commonly used media for contrast for contrast imaging procedures and interventions is the contrast which is iodinated.

Contrast media with high osmolality (HOCM) are attached with a sodium atom ionically and they give two osmotic particles on dissociation in plasma. They have iodine particles which are three in number per two osmotic particles(1.5:1).

Because of high osmolality (1500-2200 mOsm) when compared to Plasma (300 mOsm), they have decreased tolerability and increased adverse reactions.

Second generation contrast media with low osmolality (LOCM) carry iodine particles which are three in number per one osmotic particle (3:1 ratio).They are non-ionic, since they have covalent bonding.They have a osmolality which is lower (600-900 mOsm), since

the covalent bonds don't usually dissociate in plasma and thus producing a fewer osmotically active particles.

The iso-osmolar contrast media (IOCM) are non-ionic dimers having six iodine particles per osmotic particle (6:1ratio). They have a osmolality (300 mOsm) similar to plasma.

Examples:

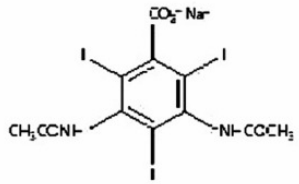
Ionic , high osmolar monomers – Diatrizoate, Metrizoate, Ioxithalamate, Iothalamate

Ionic, low osmolar dimmers - Ioxagate.

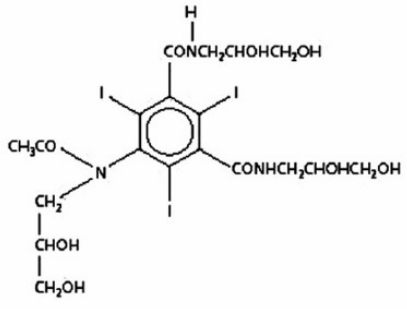
Nonionic, low osmolar monomers- Iopamidol, Iomeprol, Iopromide, Iohexol

Nonionic, iososmolar dimmers - Iodixanol

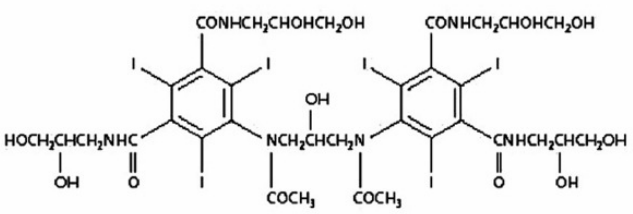
STRUCTURES OF THE CONTRAST AGENTS USED



Iothalamate



Iohexol



Iodixanol

Osmolality is dependent on the number of particles of solute dispersed in the solution and radioopacity on the iodine concentration in the solution[39,40]. Osmolality can be reduced by a decrease in the number of iodine or by using nonionic media.

Compound	**Iodine atoms**	**Particles**	**Ratio**
Ionic monomers	3	2	1,5
Non ionic monomers	3	1	3,0
Ionic dimers	6	2	3,0
Non ionic dimers	6	1	6,0

In coronary angiography or percutaneous coronary intervention, **Jo et al** study which was a randomized study done prospectively showed that 10 out of 164 patients(6.1%) in the iososmolar contrast media had CIN when compared with the low osmolar contrast group where 18 out of 117 patients (15.4%) developed CIN[41].**Solomen** study revealed that the incidence of CIN was mostly in patients who received iohexol than those who received iodixanol or iopamidol[42].It has been shown that the iososmolar contrast media have lower nephrotoxic

properties when compared to the low-osmolar media in a high risk population in the **NEPHRIC study**[43].

ADVERSE RECTIONS TO CONTRAST AGENTS

ACUTE ADVERSE EFFECTS

Allergic like reactions

Allergic like reactions to injected contrast media develop in a similar manner to that of other drugs and allergens, but it comes under anaphylactoid, allergy-like or idiosyncratic since an antigen –antibody cannot be identified. It is not dependent on the dose and the concentration of the contrast media used. Treatment is like any other allergic reaction[44,45].

Physiological reactions

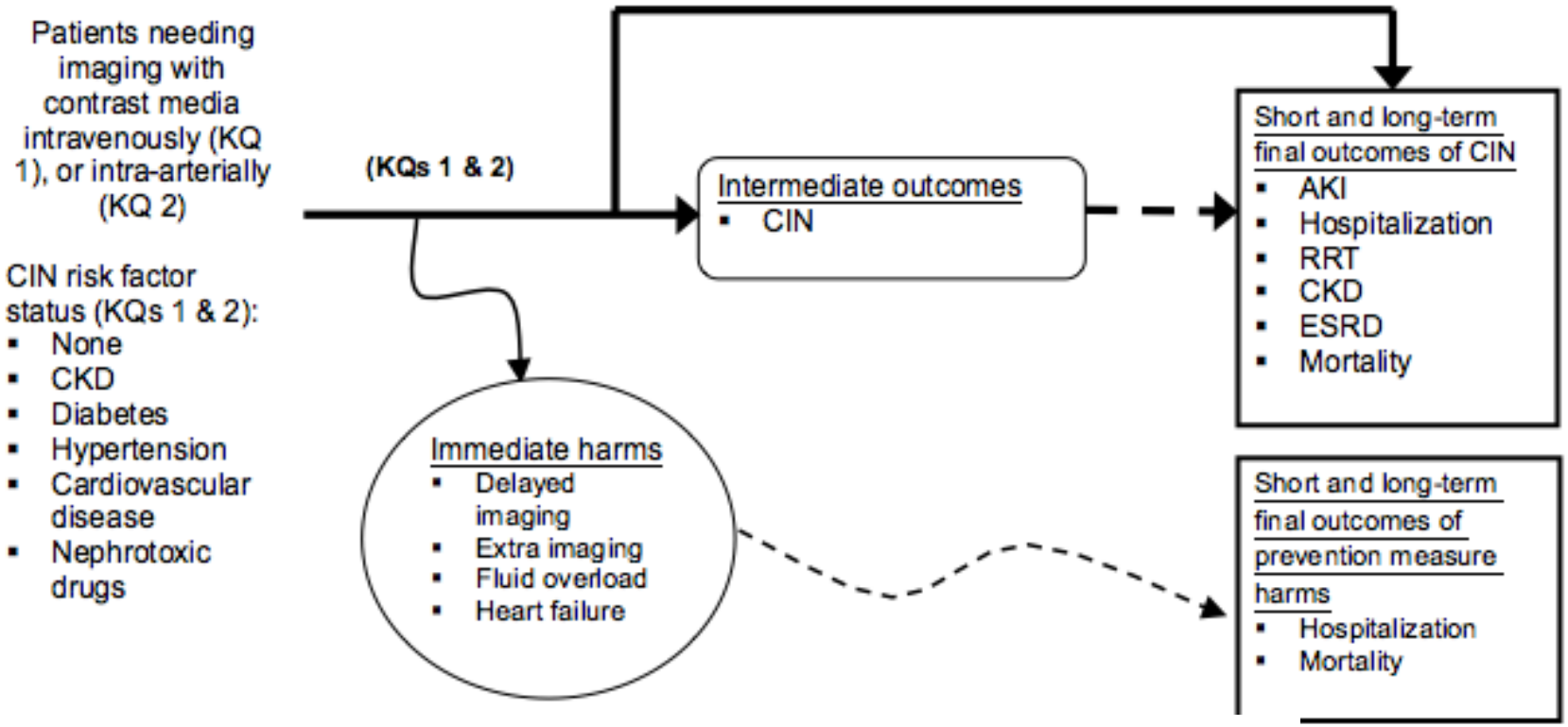
Physiological reactions are dose and concentration dependent. Cardiac arrhythmias, decreased contractility of the myocardium, cardiogenic pulmonary edema, and seizures are serious physiological reactions to iodinated contrast media and are very rare. These effects are attributed to the hyperosmolality of the contrast media and / or functional hypocalcemia due to calcium binding. Cardiac related adverse effects are more during intra-arterial than during intravenous injection of iodinated contrast media. And it is observed more in

patients with underlying cardiac disease[46,47].Non cardiogenic pulmonary edema has also been very rarely reported[48].

Vasovagal reactions as evidenced by hypotension and bradycardia are relatively quite common probably due to increased vagal tone from the central nervous system. Also there is suppressed sinoatrial and atrioventricular nodal activity, atrioventricular conduction inhibition along with vasodilatation of the peripheral vascular system. Most vagal reactions are usually mild and self-limited. Patients should be monitered carefully until they recovers completely.

Nephrotoxic effects in the form of contrast induced nephropathy is seen and is more with patients already having existing renal insufficiency.

Patients already having an underlying medical problem are more prone for adverse reactions. Bronchospasm is more common with patients having bronchial asthma. Many studies have proved that a test dose of the contrast have no role in the reduction of incidence of allergic reactions and in fact increase it. It is important to note that a non reactor to a test dose may develop a allergic reaction to the standard dose of the contrast. So, test doses for predicting reactors to contrast media used are not generally advised[49,50].

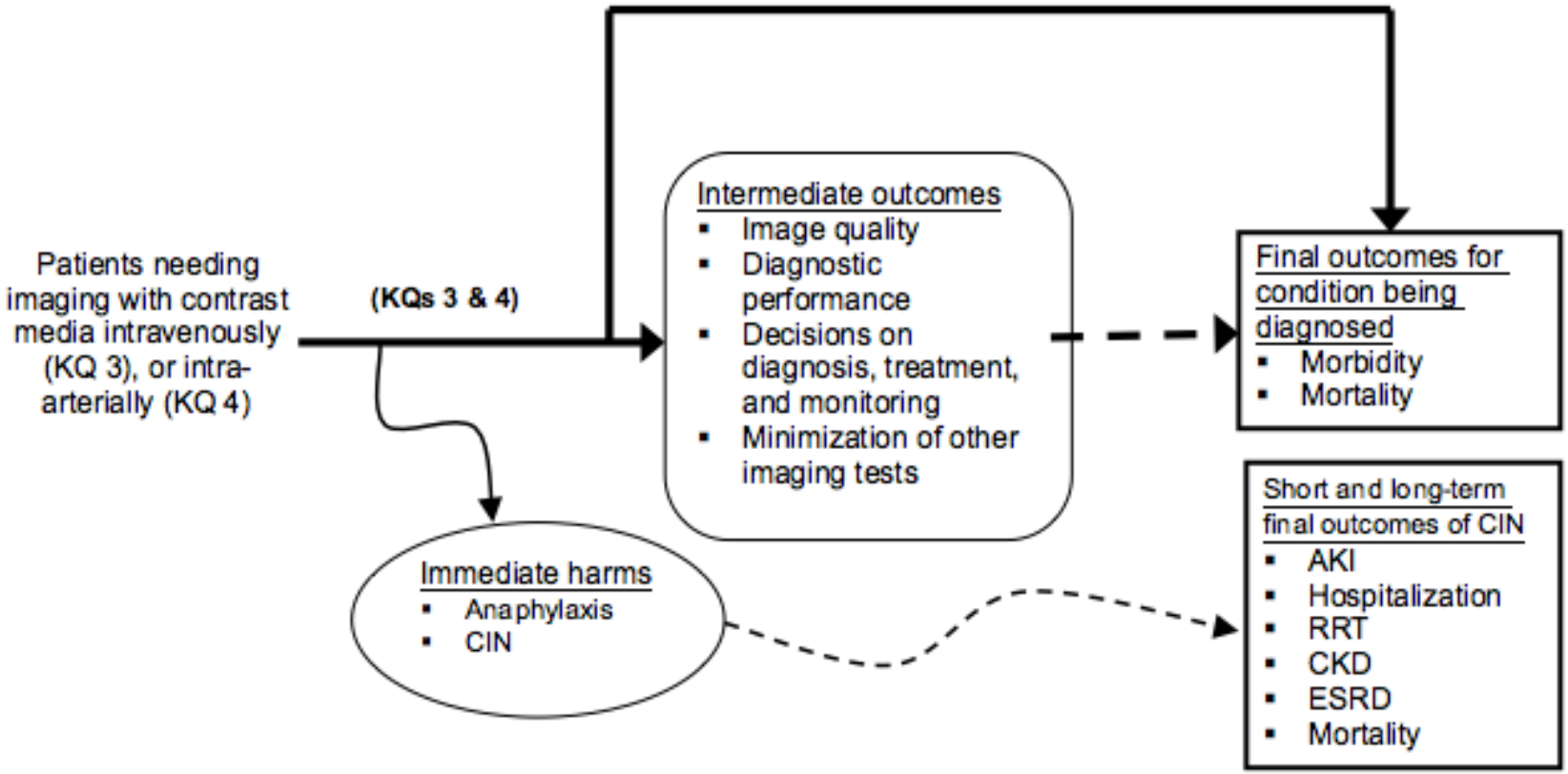


KQ – Key Questions

Analytic Frame Work Examining Intervention to prevent CIN

AKI – Acute Kidney injury **CKD – Chronic Kidney Disease**

RRT – Renal Replacement Therapy **ESRD - End Stage Renal Disease**



KQ – Key Questions

Analytic Frame Work Comparing Benefit and Harms of Different Contrast Media

A review by effective health care program was done in in Jan 2013, where seven meta-analyses done in the last 12 months on CIN were reviewed. These meta-analyses focused primarily on the incidence of CIN by route of administration of contrast media and various prevention methods. Their results are varied and conflicting, likely due to the varied inclusion criteria. Based on the increasing use of contrast media, the increasing prevalence of populations vulnerable to CIN (i.e., people having chronic kidney disease, diabetes mellitus, or hypertension, and the elderly), increasing use of radiologic and cardiologic studies, and controversial and discrepant results from various prior meta analyses, a comprehensive systematic review of this topic will be extremely valuable to clinicians who wish to minimize the risk of CIN in patients undergoing imaging studies. The following two analytical framework charts were used in the study which compared the benefits and harms of different contrast media used and also the interventions to prevent CIN.

RISK FACTORS FOR CIN

The factors that increase the occurance of CIN are either related to the patient or the contrast media used or the procedure related[51,53]

PATIENT RELATED RISK FACTORS

OLDER AGE

Explanations are attributed to the age related changes like increase in vasoconstrictive effect than the vasodilatory effect, vascular access difficulty and calcification of the vessels increasing the requirement of the contrast media used.And also the presence of associated renovascular disease.

GENDER

Females are an independent predictor of CIN explained being the ovarian hormones affecting the renin-angiotensin system and the renal blood flow.

PREEXISTING RENAL DISEASE

Chronic kidney disease usually have a decreased vasodilatory response which has a role in the development of CIN. Also the clearance of contrast media is delayed in patients with preexisting renal disease.

DIABETES MELLITUS

In patients with diabetes have alteration of Nitric-oxide mediated vasodilatation and there is reduction of renal outer medullary oxygen[54].Endothelial dysfunction is also seen in patients with diabetes and chronic kidney disease. Diabetic nephropathy is an important risk factor for CIN.

LEFT VENTRICULAR DYSFUNCTION

Decreased left ventricular ejection fraction and congestive heart failure (New York Heart Association class iii or iv) are also shown to have some role in the development of CIN[54,55].

HYPERTENSION

In hypertension, the intra renal expression of renin angiotensin system or nitric oxide which are vasoactive substances contributes to the emergence of hypertension as a risk factor .

ANGIOTENSIN CONVERTING ENZYME INHIBITORS

They have a potential in the reduction of renal function ,hence considered as a risk factor in the development of CIN as evidenced in some studies[57].It is important to check for the use of ACE inhibitors before coronary angiography.

NEPHROTOXIC DRUGS

Drugs which are toxic to kidney and the drugs which antagonise the vasodilatory effects of prostaglandins make the kidneys more prone to the toxic effects of contrast media. Sulphanamides, Aminoglycosides, Cyclosporin A,and Cisplatin are some of the drugs most commonly witnessed with nephrotoxicity,more when combined with frusemide.Non selective NSAIDS and selective COX-2 inhibitors increase the vasoconstrictive effects of contrast media by decreasing the vasodilatory prostaglandins[58,59].

METFORMIN

A decrement in the renal function after contrast media would affect the clearance of metformin, leading to development of lactic acidosis.

HYPERCHOLESTEROLEMIA

Hypercholesterolemia promotes the development of CIN by decreasing the production of nitric oxide.

HYPERURICEMIA

Tubular obstruction by uric acid has been found to have a role in the development of CIN. There is increased production of reactive

oxygen species, endothelin -1, stimulated renin-angiotensin system, and an inhibited nitric oxide ,all are involved in the development of CIN[60].

HYPOVOLEMIA

Decreased renal perfusion and decreased effective circulating volume stimulate renal vasoconstriction after exposure to contrast media. And the toxic effects of contrast media may get aggravated in the presence of hypovolemia. Also there is increased sodium reabsorption because of hypovolemia leading to vasoconstrictive stimuli depriving oxygen in the medulla[61,62].

LOW SERUM ALBUMIN LEVEL

Low serum level alters the function of endothelium, increases the renal vasoconstrictive effect, decreases the production and release of nitric oxide[63].

HEMATOCRIT LEVEL

When there is decreased level of hematocrit, there is increased incidence of CIN due to anemia induced deterioration of renal ischeamia. Each 3% decrease in hematocrit from the baseline resulted in a increase in the incidence of CIN in patients with and without

chronic kidney disease (11 and 23 % respectively).This is shown in a prospective study by **Nikolsky et al[64].Dangas et al** also showed that the hematocrit level is one of the predictors for the development of CIN in patients with chronic kidney disease[65].

MULTIPLE MYELOMA

Patients having multiple myeloma are considered to be a risk factor for the development of CIN. The mechanism proposed is that in multiple myeloma , high amount of protein in the tubular lumens of the kidneys along with concomitant load due to contrast media might cause a obstructive nephropathy. The pathomechanism of this that there is precipitation of contrast agents ,along with Tamm-Horsfall proteins and other abnormal proteins. Also because of the concomitant occurance of hyperuricemia, hypercalcemia, dehydration, amyloidosis and light chain nephropathy in multiple myeloma, patients with multiple myeloma are at increased risk of CIN when compared with others having contrast administration.

OTHER FACTORS RELATED TO THE PATIENT

1. Metabolic syndrome
2. Impaired fasting glucose and hypertriglyceridemia
3. Hypotension
4. Sepsis
5. Cirrhosis
6. Pulmonary Edema.
7. Acute myocardial infarction
8. Renal transplantation
9. Multiple coronary vessel involvement
10. Peripheral vascular involvement
11. Renal artery stenosis

PROCEDURE AND CONTRAST MEDIA RELATED RISK FACTORS

1. Increased total dose of contrast media
2. High osmolality of the contrast media
3. High viscosity of the contrast media
4. High ionic content of the contrast media
5. Intra arterial injection of the contrast media

6. Urgent or emergency procedures
7. Intraaortic ballon pump usage
8. Intervention with bypass graft and when reperfusion is delayed
9. The interval between contrast using procedures is less than two days

Generally factors contributing to the development of CIN are divided into non modifiable and modifiable risk factors

Non modifiable risk factors

Older age

Patients with pre existing renal dysfunction

Diabetus mellitus

Congestive cardiac failure with low ejection fraction

Acute myocardial infarction

H/o cardiogenic shock

H/o renal transplant

Modifiable risk factors

Volume of contrast media used

Osmolality of the contrast media used

Hemodynamic instability

Dehydration

Use of frusemide

Use of nephrotoxic drugs

Anemia and procedural blood loss

Repeat administration of contrast agent within three weeks

PREVENTION OF CIN

For the prevention of CIN either pharmacological or non pharmacological methods can be used.

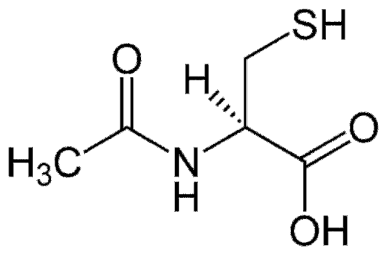
PHARMACOLOGICAL METHODS

HYDRATION

Adequate hydration before the procedure is very important in the maintenance of renal function.Thus maintaining adequate intravascular volume for renal perfusion and also preventing the occurrence of hypotension is important. There are studies regarding hydration in the

form of bolus versus continuous ,the later being found better.And oral versus intravenous form, the intravenous form being found better.

N-ACETYL CYSTEINE (NAC)



NAC may reduce vasoconstriction and oxygen free radical generation after contrast media exposure.

The **APART (Acetylcysteine to prevent Angiography –related renal tissue injury) trial** showed that N-acetylcysteine reduced the occurrence of CIN compared with the placebo group[66].However, another study by **Briguori et al** failed to show the difference in the occurrence of CIN between the patients taking N-acetylcysteine with hydration and patients given hydration alone[67].

A large multicentre randomised, placebo controlled **ACT (Acetylcysteine for contrast induced nephropathy) trial**, did not show the protective role of N-acetylcysteine in prevention of CIN[68].

DOPAMINE

Dopamine in a low dose usually has a vasodilatory effect on the blood vessels of the kidney and hence it has a protective effect on the kidneys. But ,dopamine does not show a similar effect on renal function taking contrast media[69,70].

FENOLDOPAM

Fenoldopam is a selective dopamine -1 receptor agonist that increases renal blood flow.Hence considered to decrease the incidence of CIN. However, the multicentre randomized **CONTRAST trial** did not show a reduction in the incidence of CIN with the treatment of fenoldopam[71].

THEOPHYLLINE AND AMINOPHYLLINE

Theophylline and aminophylline which are non specific adenosine (A1) receptor antagonists may decrease the blood flow to the kidneys and glomerular filtration rate stimulated after exposure to contrast media. In a study by **Huber et al**, prophylactic theophylline 200 mg given intravenously decreased the incidence of CIN when compared with the placebo. However, other studies did not reveal a relation between the prophylactic theophylline and the incidence of CIN[72,73,74].

CALCIUM CHANNEL BLOCKER

They have a favourable outcome on renal hemodynamics like reversal of renal vasoconstriction,decrease in renal hypertrophy, decrease in free radical formation,reduction of calcium overload produced by toxic or ischemic stimuli.In a study that included 35 patients, glomerular filtration rate was preserved in patients who received nitrendipine compared to patients who did not receive in whom it was decreased[75].However, in three other studies, where the effect of calcium channel blockers was studied did not show a difference[76–78].

ACE INHIBITORS AND ANGIOTENSIN RECEPTOR BLOCKERS

ACE inhibitors and angiotensin receptor blockers decrease the constriction of afferent arterioles ,also decrease medullary ischemia and thus decrease the incidence of CIN in patients undergoing contrast using procedure.Captopril was used in a study which included a small group of 71 patients with diabetes mellitus in whom coronary angiography was done.The filtration rate in the glomeruli increased in patients to whom captopril was given but decreased in patients to whom it was not given[79].However, this was not supported in another retrospective study, where the use of ACE inhibitors proved to increase

the incidence if CIN[80].Therefore, there is not enough studies or support to approve or disprove the use of ACE inhibitors or angiotensin receptors before the exposure to contrast in patients who are at high risk of developing CIN.

ATRIAL NATRIURETIC PEPTIDE

Atrial natriuretic petide was used by **Kurnik et al** in three different doses for the prevention of CIN. It did not reveal any evidence of prevention[81].

PROSTAGLANDINS E1

A study investigated the effect of prostaglandins E1 given intravenously in three different doses, since the prostaglandins cause a change in physiologic vasoconstriction/vasodilatation balance which is beneficial in decreasing the incidence of CIN. All the three group of patients showed less incline in serum creatinine when compared to the placebo group after the contrast using procedure[82].

STATINS

In two retrospective studies, pretreatment with statins was evidenced by decreased incidence of CIN[84]. However, another prospective study in 247 patients with chronic renal insufficiency did not support this evidence[83].

ASCORBIC ACID

A recent randomised trial evidenced that the use of ascorbic acid was shown to have a reduction in CIN by 62% in patients with renal insufficiency undergoing coronary angiography[(85)]

ENDOTHELIN RECEPTOR BLOCKERS

Oldroyd et al study studied the effect of bosentan, an oral endothelin antagonist, for decreasing the deterioration of renal function following contrast exposure in animal models[(93)].In **Wang et al** study, the patients were taken for cardiac angiography with a mixed endothelin A and B antagonist versus placebo.Also all the patients were hydrated with saline.The increase in creatinine from the baseline value is found to be more in patients who were treated compared with those not treated.(56% versus 29%).This is observed in both diabetic and non diabetic patients[(94)].

TRIMETAZIDINE

The mechanism behind using trimetazidine in the reduction of renal injury is by decreasing the adenosine tri phosphate intracellularly and thereby increasing the metabolism of glucose by blocking the

metabolism of fatty acid.Hence, trimetazidine with hydration was tried and it was found to be effective when compared with the placebo. More studies are required regarding formulating a protocol.

ANISODAMINE

It is a belladonna alkaloid from a Chinese herb and it is a blocker of M-choline. It is found to increase the ischemic tolerance.

PLATELET GLYCOPROTEIN IIb/IIIa RECEPTOR INHIBITORS

These drugs – abciximab, eptifbatide or tirofiban were found to increase the blood flow to the kidneys which were decreased by the contrast agents and also they increase the perfusion to the kidneys by decreasing the aggregation of platelets.

METHODS USED DURING THE PROCEDURE TO DECREASE THE EXSPOSURE TO CONTRAST WHICH IS IODINATED

Methods for decreasing the amount of contrast used during the contrast using procedures are important in that they decrease the adverse effects with the use of contrast agents proportional to the volume of contrast used, but are not much studied.

Diluting the contrast agent used is an effective and useful way in decreasing the dose of contrast media used.The dilution of 1:3 to 1:5, that is the ratio of contrast to saline when used in the procedures involving the extremities, could produce effective diagnostic imaging results.When used in the abdomen, dilution of 1:2 was sufficient to give the results.

Using digital software for enhancing the images such as image stacking software can further increase the quality of the images especially in the extremities. Also the bolus chasing technique can guide us with a single injection.

Another important technique in decreasing the volume of contrast used is the placement of the catheter. The amount of contrast needed will be decreased when we place the catheter nearer to the target.

Various other methods used to decrease the amount of contrast used include CO2 angiography, biplane angiography to get multiple images with one injection.We can also use rotational CT and intravascular ultrasound to procede the procedures and thus decreasing the volume of contrast used.

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HEMODIALYSIS

Contrast agents which are iodinated are dialyzable easily.The contrast media are cleared from the plasma at the rate of 50-70 mL/min, approximately about 80% are cleared from the plasma in about four to five hours of hemodialysis. Many studies done to see the effect of hemodialysis, in patients already having chronic kidney disease after they got exposed to contrast media, to decrease the effect on renal function, did not show any promising effect. Also studies done to see the effect of prophylactic hemodialysis, which was done just after patient got exposed to contrast did not decrease the incidence of CIN or other adverse effects[86,87].But in one study, where patients where given adequate hydration versus hydration and hemodialysis immediately after contrast exposure. Here, prophylactic hemodialysis showed less creatinine increase and decreased requirement of further renal replacement therapy[88].

HEMOFILTRATION

In one prospective study in patients with already existing renal insufficiency , hemofiltration done before and after contrast using procedure, was compared with hydration.Patient who underwent hemofiltration alone showed decreased incidence of CIN, decreased

requirement of renal replacement therapy, decreased mortality both in hospital and also in one year[89].

TARGETED RENAL TREATMENT

Here the therapeutic drugs are given to the kidneys using a separated infusion machine. Here there is increased and persistant levels of medicines in the kidney and thus decreasing the adverse effects. There was a study done in 285 patients who were at increased chance for getting CIN, where fenoldopam was given into the renal arteries ,were found to have a lower incidence of CIN.

HYPOTHERMIA

The incidence of renal damage post contrast study in patients with neurological damage and association with hypothermia was studied in a trial of 128 patients with a maintenance of core temperature of 33 to 34 degree centigrade versus normal temperature, found that there is no variation in the occurrence of renal damage between normothermic and hypothermic patients.

ISCHEMIC PRECONDITIONING

It means that by creating brief intermittent ischemia in the nontarget organs vascular bed, and hence protecting the target organ. The method starts before the contrast using procedure with four

cycles of alternating five minutes inflation and five minutes of deflation of blood pressure cuff .The result in the form of elevation of serum creatinine from the baseline value within 48 hours was taken.The incidence of renal injury was found to be less in the persons who underwent ischemic preconditioning. Serum cystatin and urinary NGAL were also found to be less in the limb maintained with ischemic preconditioning. The possible explanations for the result could be due to inflammatory and anti-inflammatory genes involved and also there could be some vasodilation involved.

ALTERNATIVE IMAGING STUDIES

Alternative methods of diagnostic studies without iodinated contrast media should be considered in patients with risk factors such as ultrasonography, scintigraphy, CT without contrast,and Magnetic resonance imaging. The use of non enhanced CT in the diagnosis of clinical cases should be thought of before subjecting them to contrast exposure.

Summary of some of the Preventive methods used for the prevention of CIN, both pharmacological and Non pharmacological.

Preventive strategies	**Efficacy**
Pharmacological strategies	
Hydration	Beneficial
Sodium bicarbonate	Inconsistant data
Furosemide	May be harmful
N acetyl cysteine	Inconsistant data
Mannitol	May be harmful
Fenoldapam	No benefit
Dopamine	No benefit
Statins	May be beneficial
Atrial natriuretric peptide	No benefit
Theophylline/Aminophylline	Inconsistant data
Calcium channel blockers	Inconsistant data
ACE inhibitors/Angiotensin receptor blockers	Inconsistant data
Prostaglandin E1	May be beneficial
Non pharmacological strategies	
Hemodialysis	Inconsistant data
Hemofiltration	May be beneficial
Benephit infusion system	May be beneficial
Renal guard system	May be beneficial

GUIDELINES USED FOR PREVENTING CIN

HYDRATION WITH SALINE[90]

Calculation of intravenous fluid used = 1ml/kg/hr (maximum 100ml/hr) 12 hours before and 12 hours after contrast (totally 24 hours as infusion)

In patients with congestive heart failure or having decreased ejection fraction <40%,- 0.5 ml/kg/hr (maximum 50 ml/hr) 12 hours before and 12 hours after contrast (totally 24 hours infusion) can be given.

For emergency procedure

Bolus of around 500-1000ml of fluid before the procedure should be given.Hydration should be done during the procedure and continued 12 hours post procedure (according to the clinical status)

GUIDELINES FOR USING BICARBONATE[91]

Intravenous fluid in the form 5%Dextrose with 150 meq of sodium bicarbonate at the rate of 3ml/kg stat dose one hour before the procedure and 1ml/kg /hour (maximum 100ml/hr) during and for 6 hours after the procedure. But in patients with diabetes mellitus sterile water can be used in the place of 5% Dextrose water .

GUIDELINES FOR USING N-ACETYL CYSTEINE[92]

If patients are taking orally, 600-1200 mg capsules are given every 12 th hourly ,totally for 4 doses.It is better to give 2 doses before the procedure and 2 doses after the procedure.

If patients are on feeding tubes or nasogastric tubes, N-acetyl cysteine is given in the form of solution as 3ml of 20% solution which contains 600-1200 mg every 12 th hourly, for totally 4 doses.

If the patient is taken for emergency procedure, one dose of N-acetyl cysteine should be given before the procedure and 3 doses post procedure is given.

Intravenous form of N-acetyl cysteine can also be given in patients in high risk patients who cannot be given orally, in the dose of 600-1200 mg IV one dose over a period of 15 minutes, 600-1200mg every 12 th hourly for 4 doses.

Other drugs which can also be given are

- Ascorbic acid in the dose of 3gm intravenously over 2 hours before the procedure and 2 gm x 2 doses following the procedure.
- Aminophyline 300 mg intravenously given over a period of 1 hour before the procedure.

CLINICAL FEATURES AND INVESTIGATIONS IN CIN

Epithelial cells in urine, calcium oxalate and urate crystals in urine are non specific findings seen in contrast induced nephropathy. Low urinary sodium and fractional excretion of sodium are considered as distinctive features of CIN , but they are not shown to be specific for CIN.

CIN is usually non oliguric and asymptamatic with a transient decrease in renal function. The value of serum creatinine rises within 24 hours post contrast procedure with attaining peak in 3- 5 days and usually returns to baseline in 10- 14 days. Rare situations are there where hemodialysis is needed for oliguric acute renal deterioration. This is manifested as oliguria (less than 400 ml of urine volume in 24 hours), within 24 hours of post contrast exposure and persists for 2 – 5 days.Mortality and morbitidy are proportionately higher in these group of patients who had undergone hemodialysis when compared with the patients who have non oliguric renal failure.

Treatment of CIN begins with the early recognition of renal dysfunction ,post study. In patients with high risk factors, serum creatinine should be monitored before the procedure and daily for 5

days post procedure. Once CIN is diagnosed, further treatment is similar to that of acute renal failure resulting from any other cause.Monitering of serum electrolytes for the presence of hyperkalemia, hyponatremia, hypocalcemia, hypermagnesemia, hyperphosphatemia and metabolic acidosis is required as in patient .Intake- output of fluids, with proper nutritional support are necessary until serum creatinine value returns to baseline. Hemodialysis which is temporary will be required in severe cases. A minority of patients who are not responding to conservative line of management may require permanent dialysis or renal transplantation.

To assess the combined risk of multiple variables on renal function, a simple CIN risk score was developed for assessing the risk of CIN and the risk of dialysis in patients undergoing PCI. The risk factors included were hypotension, IABP, CHF, Age >75 years, Anemia, Diabetes, Volume of contrast media, Serum creatinine or eGFR. The assessment of the risk for CIN post-PCI in a simple way with the readily available information makes widespread use of this risk score for both clinical and investigational purpose.

Risk prediction score for the development of contrast induced nephropathy and renal failure requiring dialysis		
Risk factors		Integer score
Hypotension		5 points
Use of intra-aortic balloon bump		5 points
Congestive heart failure		5 points
Age >75 years		4 points
Anemia		3 points
Diabetic mellitus		3 points
Volume of contrast media		1 point for each 100 ml used
S.creatinine >1.5 mg/dl		4 points
Or		
eGFR 60ml/min/1.73 m2		
		2 points for 40-60 4 points for 20-40 6 points for <20
Risk assessment		
Risk score	Risk of CIN	Risk of dialysis
5 points	7.5%	0.04%
6–10 points	14%	0.12%
11–16 points	26.1%	1.09%
16 points	57.3%	12.6%

IMPLICATIONS OF CIN

Clinical implications of renal function deterioration post exposure to contrast agent were studied in many trials. A key factor in the identification of even a small deterioration in the renal function can lead to a dramatic effect on the prognosis.

Another study which included 19,982 patients showed that a smaller increase in serum creatinine was associated with increased mortality , increased length of hospital stay and increased cost of treatment.

MATERIALS AND METHODS

STUDY POPULATION

The study included 102 patients who had coronary angiogram in the Cardiology Department in the Government Stanley Medical College from June2013 to August2013 .

STUDY DESIGN

Age and gendor of the patients noted.

Patients were taken as hypertensives if they were already under antihypertensives or newly diagnosed if their blood pressure was above or equal to 140/90 mmHg according JNC 7 criteria.

Patients who were already taking oral hypoglyceamics or on subcutaneous insulin preparations or newly diagnosed with the random blood sugar >200 mg /dl or with a fasting blood sugar >126mg/dl were noted as diabetics.

Patients who smoke tobacco in any form irrespective of number of years were noted as smokers.No criteria was followed.

The hydration of the patient was clinically examined. No regime was followed for hydrating the patients if they were found to be dehydrated.

The drug history of the patient especially nephrotoxic drug intake was asked namely ACE inhibitors, Diuretics, Analgesics in the form of NSAIDS, and any nephrotoxic antibiotics recently for any illness were noted down.

The haemoglobin status of the patient was noted down.Patient was considered as anaemic if the haemoglobin level was below 12 gms% in females and 13 gms% in males according to WHO criteria.

Volume of the contrast media used during the coronary angiogram study was between 30-50 ml.None of the study used the contrast media above 50 ml.The contrast used was iohexol which is non-ionic, water soluble contrast media which contains 17.5 gms of Iodine in 50ml.

Renal function of all patients undergoing the coronary angiogram were assessed with the values of serum creatinine, blood urea, urine routine examination and examining with the ultrasound for the kidney size and corticomedullary differentiation. And patients with altered renal parametres were not included in the study.

The values of serum creatinine before the angiogram was taken. And the serum creatinine was repeated after 48 hours of the study for any change in the value and noted down.

The patients were under strict observation to look for any allergic or adverse reactions in any form during the use of the contrast in the study.No such reactions were seen during the study or after the study.

Patients were all informed about the study and the adverse reactions of the contrast used and written informed consent obtained before subjecting to the procedure.

No regime or protocol was followed before and after the study for preventing the incidence of CIN. And since this is an observational study.

STATISTICAL ANALYSIS

The datas collected from the patients were age and gendor of the patients ,smoking history, presence of hypertension, presence of diabetes mellitus, intake of ACE inhibitors, Diuretics, Non steroidal anti inflammatory drugs, Nephrotoxic antibiotics ,volume of the contrast media used, hydration status of the patient, and hemoglobin percentage .

Descriptive statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean $\pm$ SD and results on categorical measurements are presented in percentage (%). Chi-square test has been used to find the significance of study parameters on categorical scale between two groups. Student 't' test has been used to determine the significance between two group means. All analyses were two tailed and $p < 0.05$ was considered significant. SPSS version 16.0 was used for data analysis.

OBSERVATIONS

The following are the contributions made by the risk factors that we included in the study

Age

		Frequency	Percent
Age	<75 yrs	100	98.0
	>=75	2	2.0
	Total	102	100.0

Table 1 : Age distribution in the study population

Patients below 75 years were 98% and patients more than or equal to 75 years were 2 % in our study

Gender

		Frequency	Percent
Gender	Male	79	77.5
	Female	23	22.5
	Total	102	100.0

Table 2 : Gender distribution in the study population

Male patients participated in our study were 77.5% and females were 22.5%

Smokers

		Frequency	Percent
Smoker	Yes	38	37.3
	No	64	62.7
	Total	102	100.0

Table 3 : Smokers Distribution in the study population

Smokers versus Non smokers -37.3% versus 62.7%

HT

		Frequency	Percent
HT	Yes	35	34.3
	No	67	65.7
	Total	102	100.0

Table 4 : Hypertensive Patients in the Study population

Hypertensive patients were 34.3 % and non hypertensives were 65.7%

DM

		Frequency	Percent
DM	Yes	35	34.3
	No	67	65.7
	Total	102	100.0

Table 5 : Diabetic Patients in the Study Population

Diabetic patients were 34.3% and non diabetic patients were 65.7 %

ACE INHIBITORS

		Frequency	Percent
ACE inhibitor use	Yes	33	32.4
	No	69	67.6
	Total	102	100.0

Table 6 : ACE inhibitors users in the study Population

Patients who were using ACE inhibitors were 32.4% and the remaining 67.6% were not using it.

DIURETICS

		Frequency	Percent
Diuretics usage	Yes	13	12.7
	No	89	87.3
	Total	102	100.0

Table 7 : Diuretics users in the Study Population

Patients using diuretics at the time of study were 12.7 % and those not using were 87.3%

NSAIDS

		Frequency	Percent
NSAID	Yes	27	26.5
	No	75	73.5
	Total	102	100.0

Table 8: NSAID users in the Study Population

Patients on NSAIDS were 26.5% and who were not were 73.5%

NEPHROTOXIC ANTIBIOTICS

		Frequency	Percent
Nephrotoxic antibiotics	Yes	4	3.9
	No	98	96.1
	Total	102	100.0

Table 9 : H/0 Nephrotoxic Antibiotics in the Study Population

Patients with the recent history of intake of nephrotoxic antibiotics were found to be 3.9% and patients with the negative history were 96.1%

DEHYDRATION

		Frequency	Percent
Dehydration	Yes	11	10.8
	No	91	89.2
	Total	102	100.0

Table 10 Dehydrated Patients in the Study Population

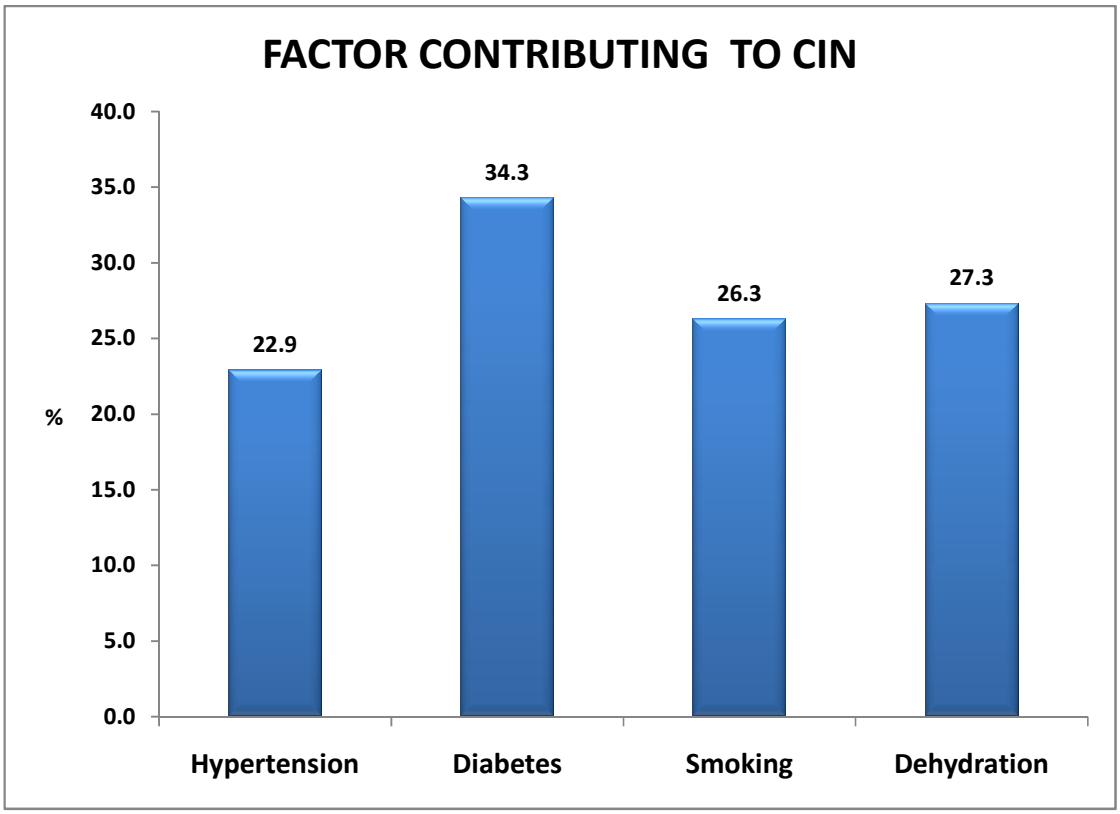
10.8% of our patients under study were found to be dehydrated and remaining 89.2% were found to be hydrated adequately.

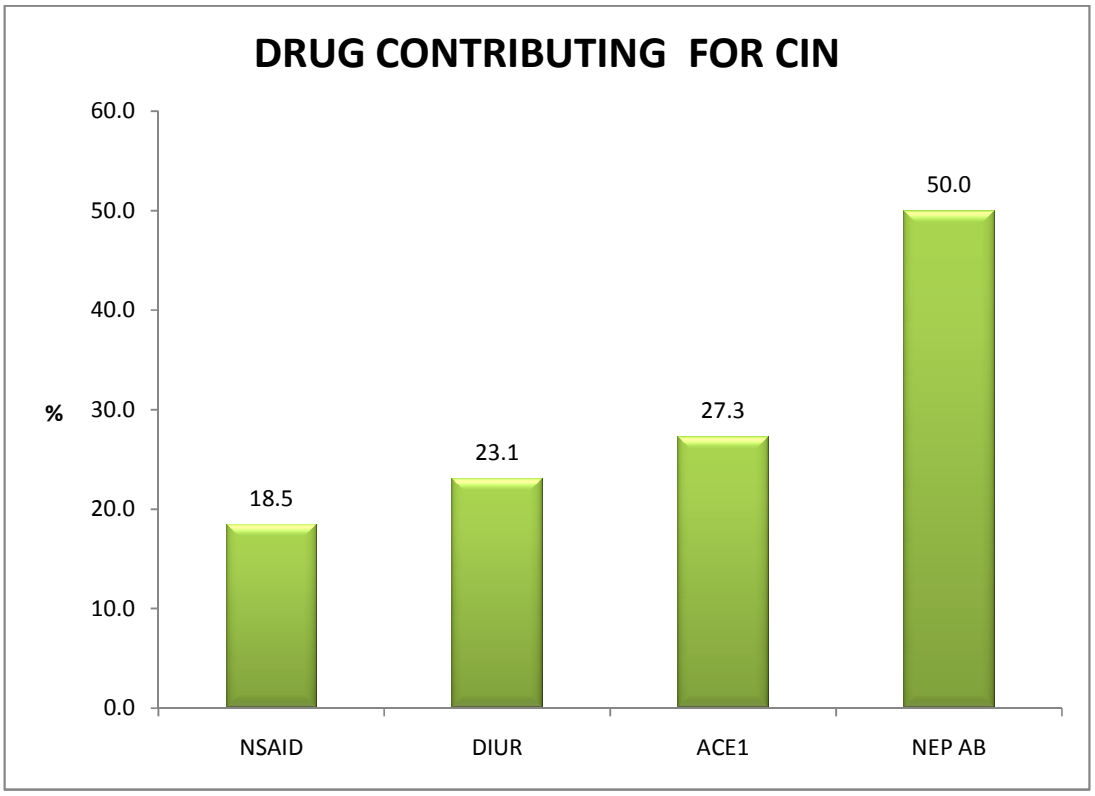
Hamoglobin

	Frequency	Percent
Anemia	86	84.3
Non anemia	16	15.7
Total	102	100.0

Table 11 Anemia percentage in the Study Population

Patients with haemoglobin less than 12 gms% in females and less than 13gms% in males is 84.3% and the patients who were not anemic were found to be 15.7%


FACTOR CONTRIBUTING TO CIN
40.0
35.0
30.0
25.0
20.0
15.0
10.0
5.0
0.0
%
22.9
34.3
26.3
27.3
Hypertension
Diabetes
Smoking
Dehydration


DRUG CONTRIBUTING FOR CIN
60.0
50.0
40.0
30.0
20.0
10.0
0.0
%
18.5
23.1
27.3
50.0
NSAID
DIUR
ACE1
NEP AB

INTERPRETATION OF EACH FACTOR'S CONTRIBUTION TO THE DEVELOPMENT OF CIN

AGE AND CIN

			CIN		Total
			Yes	No	
age_75gp	<75 yrs	Count	22	78	100
		% within age_75gp	22.0%	78.0%	100.0%
	>=75	Count	1	1	2
		% within age_75gp	50.0%	50.0%	100.0%
Total		Count	23	79	102
		% within age_75gp	22.5%	77.5%	100.0%

The proportion of CIN is higher in patients <75 years, and it is not statistically significant.(p value =0.402).Also our concern is the number of patients above 75 years who more prone for CIN contributed only 2% of our study. Hence their contribution could not be studied.

SMOKERS AND CIN

			CIN		Total
			Yes	No	
Smoker	Yes	Count	10	28	38
		% within Smoker	26.3%	73.7%	100.0%
	No	Count	13	51	64
		% within Smoker	20.3%	79.7%	100.0%
Total		Count	23	79	102
		% within Smoker	22.5%	77.5%	100.0%

Contribution by smokers to the development of CIN was 26.3% with a p value of 0.625 which is statiscally not significant

DM AND CIN

			CIN		Total
			Yes	No	
DM	Yes	Count	12	23	35
		% within DM	34.3%	65.7%	100.0%
	No	Count	11	56	67
		% within DM	16.4%	83.6%	100.0%
Total		Count	23	79	102
		% within DM	22.5%	77.5%	100.0%

Of the 35 Diabetic patients in our study 12 patients were found to have CIN which corresponded to the percentage of 34.3 % with a significant p value of 0.049 and it is statiscally significant.This is the risk factor which contributed much to the development of CIN in our study.

HT AND CIN

			CIN		Total
			Yes	No	
HT	Yes	Count	8	27	35
		% within HT	22.9%	77.1%	100.0%
	No	Count	15	52	67
		% within HT	22.4%	77.6%	100.0%
Total	Count		23	79	102
	% within HT		22.5%	77.5%	100.0%

The incidence of CIN in the hypertensive patients in our study is 22.9% with a p value of 1.000, which is statiscally not significant.

ACE INHIBITORS AND CIN

			CIN		Total
			Yes	No	
ACE 1	Yes	Count	9	24	33
		% within ACE 1	27.3%	72.7%	100.0%
	No	Count	14	55	69
		% within ACE 1	20.3%	79.7%	100.0%
Total		Count	23	79	102
		% within ACE 1	22.5%	77.5%	100.0%

ACE inhibitors users in our study group were around 32.4 % and their contribution to CIN is around 27.3% with a p value of 0.455, which is statiscally insignificant.

DIURETICS AND CIN

			CIN		Total
			Yes	No	
DIUR	Yes	Count	3	10	13
		% within DIUR	23.1%	76.9%	100.0%
	No	Count	20	69	89
		% within DIUR	22.5%	77.5%	100.0%
Total		Count	23	79	102
		% within DIUR	22.5%	77.5%	100.0%

Out of the 12 patients of 102 patients who were using diuretics at the time of study, the incidence of CIN is 23.1% with a p value of 1.000 which is statiscally insignificant.

NSAIDS AND CIN

			CIN		Total
			Yes	No	
NSAID	Yes	Count	5	22	27
		% within NSAID	18.5%	81.5%	100.0%
	No	Count	18	57	75
		% within NSAID	24.0%	76.0%	100.0%
Total		Count	23	79	102
		% within NSAID	22.5%	77.5%	100.0%

The number of patients who were using NSAIDS at the time of study were 26.5 % and their contribution to the incidence of CIN is18.5% with a p value of 0.789, which is statiscally insignificant.

NEPHROTOXIC ANTIBIOTICS USAGE AND CIN

			CIN		
			Yes	No	Total
NEP AB	Yes	Count	2	2	4
		% within NEP AB	50.0%	50.0%	100.0%
	No	Count	21	77	98
		% within NEP AB	21.4%	78.6%	100.0%
Total		Count	23	79	102
		% within NEP AB	22.5%	77.5%	100.0%

The percentage of patients who were on nephrotoxic within recently before the procedure were only 3.9% and the contribution by their usage to CIN is 50.0% with a value of 0.218 which is statiscally insignificant**.**

DEHYDRATION AND CIN

			CIN		Total
			Yes	No	
DeHy	Yes	Count	3	8	11
		% within DeHy	27.3%	72.7%	100.0%
	No	Count	20	71	91
		% within DeHy	22.0%	78.0%	100.0%
Total		Count	23	79	102
		% within DeHy	22.5%	77.5%	100.0%

The percentage of dehydrated patients in our study were 10.8% and the contribution by them to the ocurrance of CIN is 27.3 % with a p value of 0.708 which is statiscally insignificant.

HEMOGLOBIN IN MALES AND CIN

Gender				CIN		Total
				Yes	No	
Male	hb_group	Anemia	Count	19	48	67
			% within hb_group	28.4%	71.6%	100.0%
		Non anemia	Count	1	11	12
			% within hb_group	8.3%	91.7%	100.0%
	Total		Count	20	59	79
			% within hb_group	25.3%	74.7%	100.0%

The incidence of CIN in male patients who were anemic is found to be 28.4% out of 77.5% male patients studied with a p value of 0.277 which is statiscally not significant.

HEMOGLOBIN IN FEMALES AND CIN

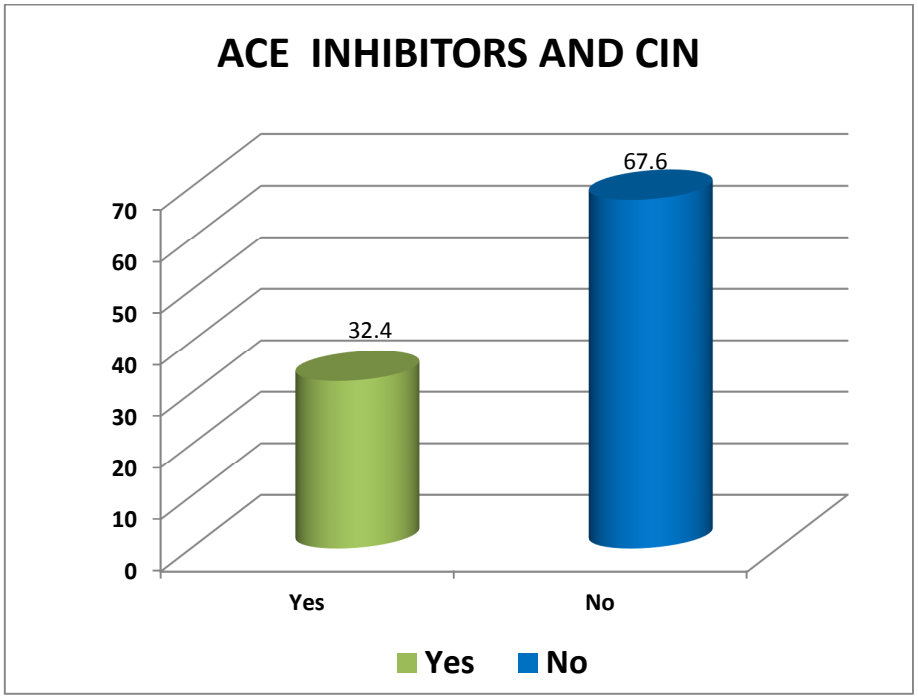
Gendor				CIN		Total
				Yes	No	
Female	hb_group	Anemia	Count	3	16	19
			% within hb_group	15.8%	84.2%	100.0%
		Non anemia	Count	0	4	4
			% within hb_group	.0%	100.0%	100.0%
	Total		Count	3	20	23
			% within hb_group	13.0%	87.0%	100.0%

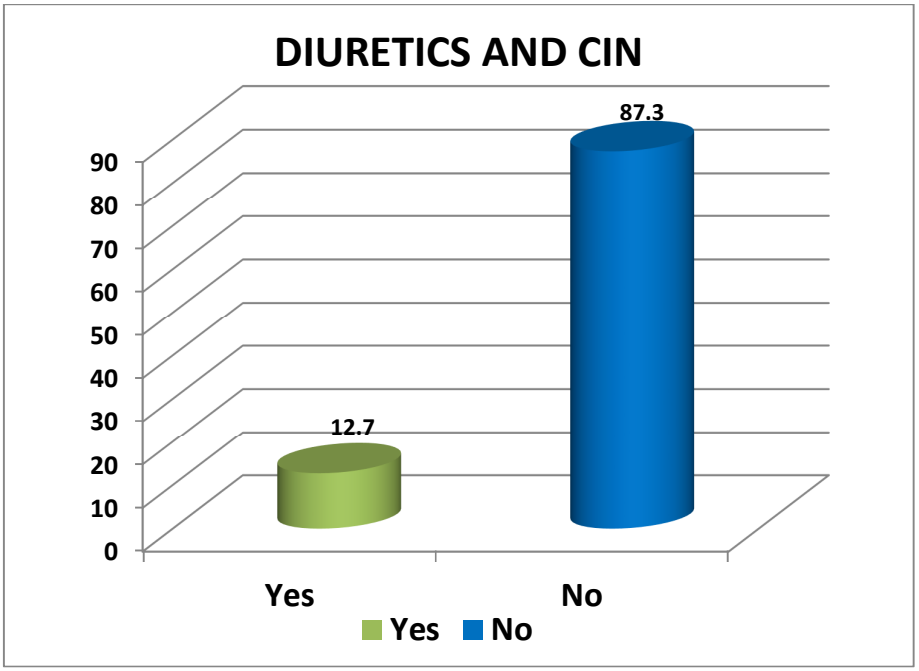
The incidence of CIN is 15.8% out of 22.5% female patients studied with a p value of 1.000 which is not statiscally significant**.**

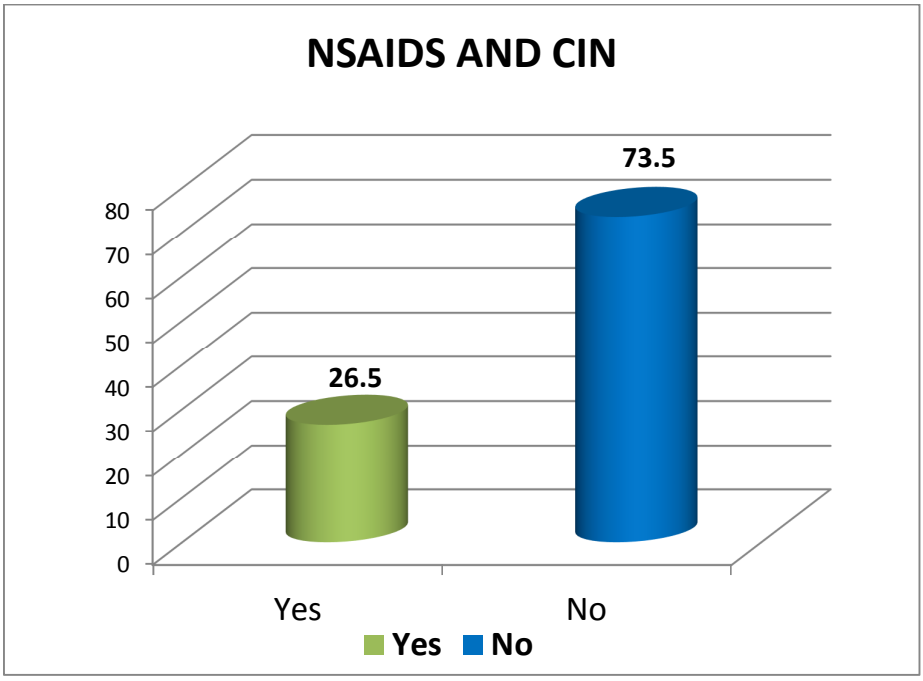
HEMOGLOBIN AND CIN

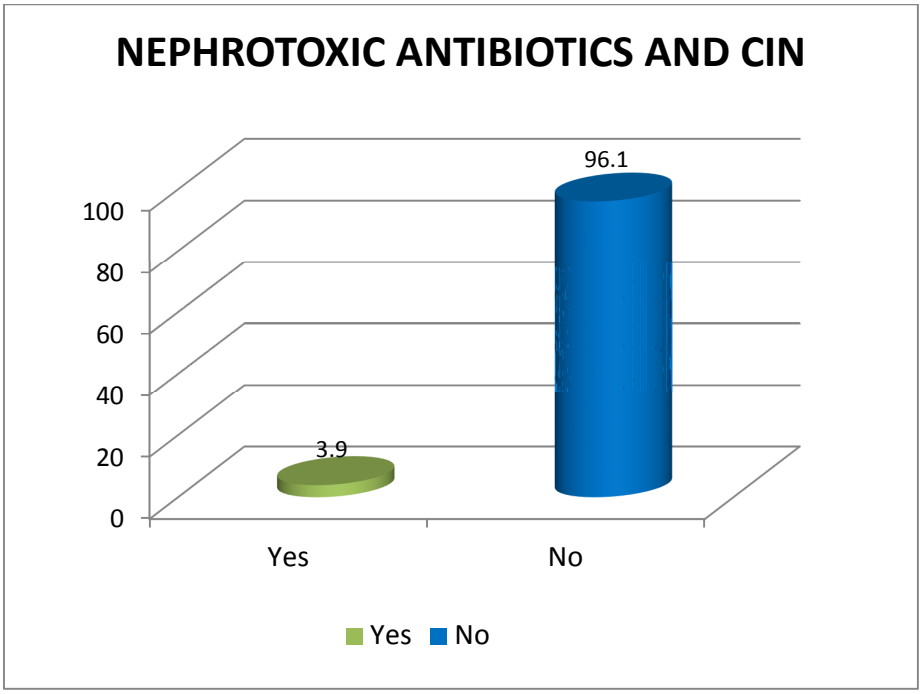
			CIN		Total
			Yes	No	
hb_group	Anemia	Count	22	64	86
		% within hb_group	25.6%	74.4%	100.0%
	Non anemia	Count	1	15	16
		% within hb_group	6.2%	93.8%	100.0%
Total		Count	23	79	102
		% within hb_group	22.5%	77.5%	100.0%

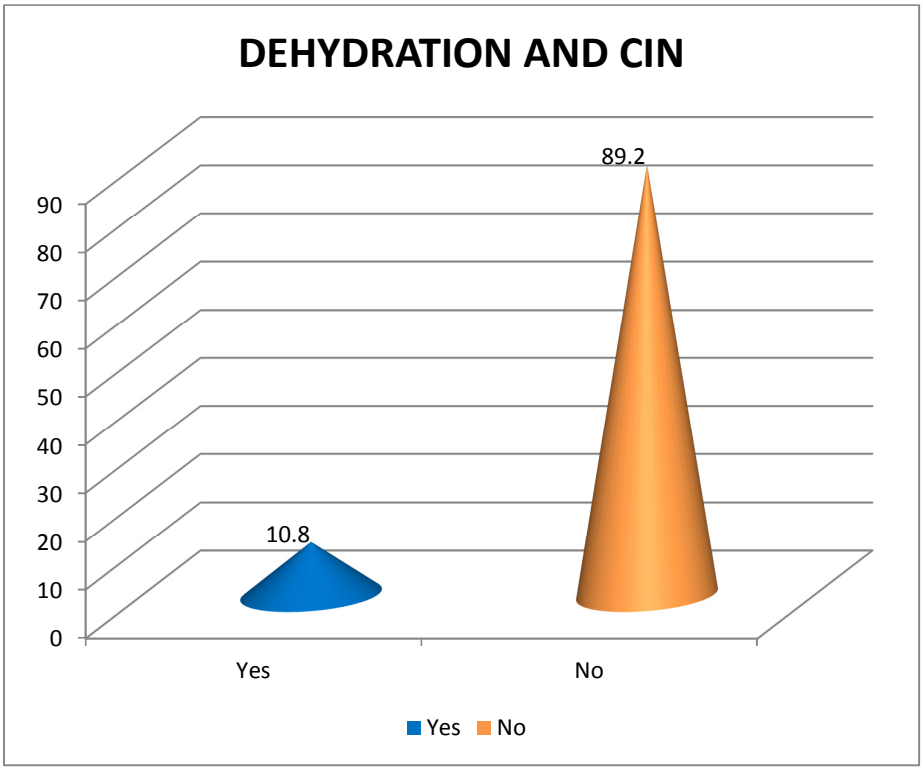
The percentage of patients who were anemic according to WHO criteria in both males and females were around 84.3 %,with the contribution to the ocurrance of CIN by males to 24.8% and by the females to 15.8% and the combined contribution being 25.6% with a p value of 0.112.And this is statiscally insignificant.

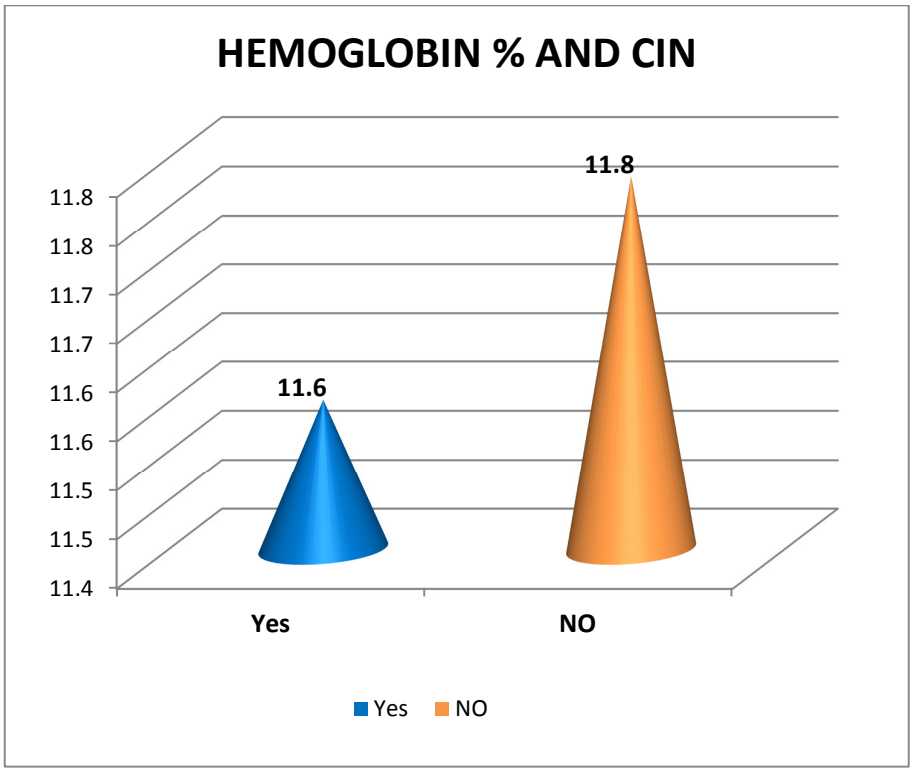

ACE INHIBITORS AND CIN
67.6
32.4
70
60
50
40
30
20
10
0
Yes
No
Yes
No

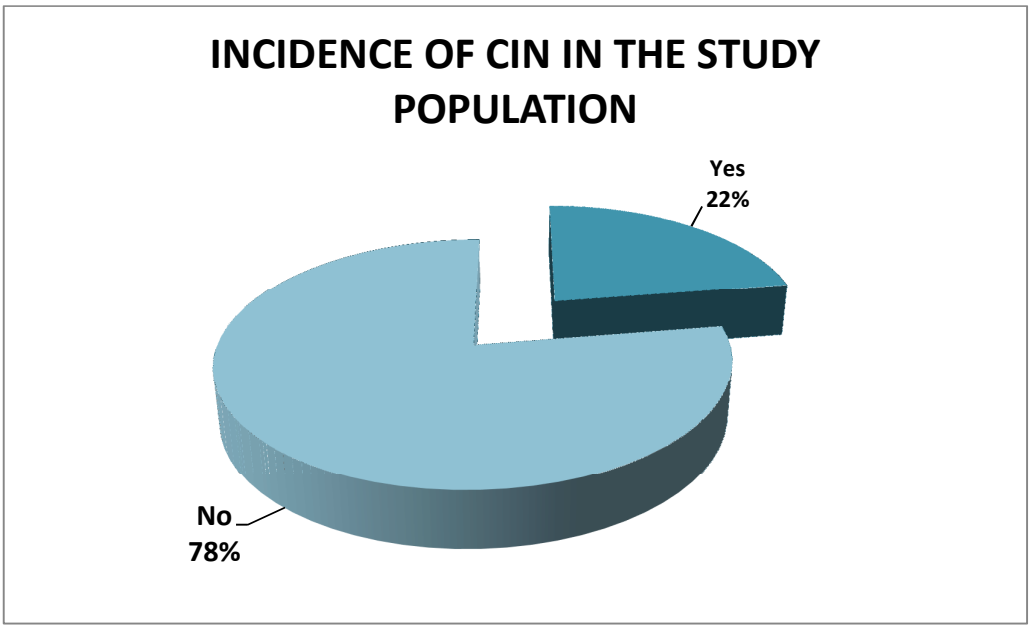

DIURETICS AND CIN
87.3
12.7
90
80
70
60
50
40
30
20
10
0
Yes
No
Yes
No


NSAIDS AND CIN
73.5
26.5
80
70
60
50
40
30
20
10
0
Yes
No
Yes
No


NEPHROTOXIC ANTIBIOTICS AND CIN
96.1
3.9
100
80
60
40
20
0
Yes
No
Yes
No


DEHYDRATION AND CIN
89.2
10.8
90
80
70
60
50
40
30
20
10
0
Yes
No
Yes
No


HEMOGLOBIN % AND CIN
11.8
11.6
11.8
11.8
11.7
11.7
11.6
11.6
11.5
11.5
11.4
Yes
NO
Yes
NO


INCIDENCE OF CIN IN THE STUDY POPULATION
Yes
22%
No
78%

DISCUSSION

Our study showed the incidence of contrast induced nephropathy in patients undergoing contrast using procedure coronary angiogram with normal renal function in our hospital.

The incidence of contrast induced nephropathy in our study was found to be 22.5%.

The patients who underwent study were with normal renal function. The patients with elevated renal parameters were excluded from the study. Hence the incidence of CIN in patients with already existing renal function could not be studied. Also since no prophylactic measures were followed in our study , the effects of any prophylactic measures could not be studied.

McCullough PA et al study showed an elevation of serum creatinine in 14.5% of patients who had coronary artery imaging studies [(1)]**. Iakovou I et al** study showed elevation of serum creatinine in 16.5% of patients[(8)] and his study also reported more number of CIN in female patients. Our study had 23 % of females and the occurrence

of CIN was 22.5% among them which is lower than the incidence in males that is 77.5% .This is not similar to the Iakovou I et al study.

Many studies which were done on CIN showed increased incidence of CIN to be increased with increasing age. Patients with age >75 years are at more risk of developing CIN compared with patients of <75 years.**Mehran et al** study done in 2004 showed the incidence of CIN in patients with age >75 years to be of 21.8%[52].In our study of 102 patients, patients with age >75 years is only one patient and another patient had the age equal to 75 years. Hence incidence of CIN in accordance with the age could not be studied in our study.

One of the most important factor contributing to the incidence of CIN is osmolality of the contrast media and it is evidenced in many studies. **Rudnick et al** studied the occurrence of CIN in 1196 patients in a prospective manner witnessed no difference in the incidence of CIN between patients who had low osmolar contrast media versus patients who had high osmolar contrast media ,who had coronary angiogram. This is the incidence in patients who were non –diabetic.But in patients who were diabetic with already existing renal insuffiency in the form of elevated serum creatinine the use of low osmolar contrast media is

associated with decreased incidence of CIN when compared with the usage of high osmolar contrast media[15]. Another study by **Barrett and Carlisle** associated the occurrence of renal injury with the use of contrast agents in 14 trials and found that the incidence of CIN was more in patients who had contrast using procedures with high osmolar agent than in the patients who had the procedures with low osmolar contrast agent, especially in patients with already existing renal dysfunction[39]. Another study by **Aspelin et al** in 2003 showed the above result[43]. Our study used only low osmolar contrast agent and hence the effect of osmolality of the contrast media on the incidence of CIN could not be studied.

Another factor which is considered to be one of the important contributing factor in the occurrence of CIN is the volume of contrast media used[5,95]. **Rihal et al** study in more than 7000 patients showed each 100 ml contrast media to increase the ratio of CIN by 1.12.[5]

Our study limited the use of contrast media to a lesser volume of 30-50 ml only. Hence the relation to the occurrence of CIN with the effect of increased volume of contrast media could not be studied.

Underlying renal dysfunction is one of the important contributing factor for the occurrence of CIN. Many studies like **Rihal et al** study[5] and **Murphy SW et al** study[96] have clearly showed the relation. Since in our study we had excluded the patients with already existing renal dysfunction, this factor could not be studied.

Diabetes was an important contributing factor in the incidence of CIN. Many studies have showed that. **Mehran et al** study showed that the incidence was around 12.5 %[52]. **Gussenhoven MJ et al** [97] study and **Gruberg et al**[6] study showed an incidence of 5%-30% among diabetic patients. Our study showed that the diabetes is an important contributing factor in the ocurrnce of CIN. The incidence of CIN in diabetic patients was found to be 34.3 % and it is statiscally significant with a p value of 0.049.

Hypertension is also an important contributing factor in the ocurrance of CIN. **Iakovou I et al** study [8], **Mehran et al**[52] study are some of the studies which showed the contribution of hypertension in the occurrence of CIN. However the study by **Gruberg L et al** [6] did not show the contribution by hypertension to the occurrence of CIN. Our study did not show a statiscally significant relationship between hypertension and contrast induced nephropathy.

Use of nephrotoxic antibiotics and analgesics- NSAIDS and the incidence of CIN were studied by **Louis BM et al** [57] and **Kolonko et al** [59]. They were found to be associated with the incidence of CIN. Our study did not show a statiscally significant relationship between the use of nephrotoxic antibiotics or NSAIDS.

Umruddin Z study[100] showed the incidence of CIN is increased in patients using ACE inhibitors or Angiotensin receptor blockers with the incidence of 4.55%.In our study ,there is no significant association made out.

Smokers in our study were 38%. The incidence of CIN in smokers is 26.3% and it is not stastiscally significant in our study.Smoking history has been included in many studies as one of the patient related risk factor and its contribution in the incidence of CIN has been shown.

Studies stating hydration versus no hydration not done previously because of lack of a placebo substitute for an intravenous hydration. In our study the number of patients who were dehydrated at the time of study were 11%. The contribution of these patients to the development of CIN was 27.3% with a p value of 0.708 which is statiscally insignificant. We did not follow any hydration protocols.

Dehydration and the presence of congestive cardiac failure are predisposing factors causing decreased perfusion to kidneys ,and thus increasing the ischaemic injury with the contrast media use.Dehydration status is particularly important in patients with multiple myeloma , where the occurrence of CIN is more with patients in dehydration.

In a study by **Murakami R et al** ,where the effect of anemia in the occurrence of CIN in patients with already existing renal dysfunction, found that low haemoglobin level remained an independent predictor of CIN, with the incidence rate of 7.8% CIN in anemic patients[98]. In **Li WH et al** study, where 1,026 patients undergoing PCI were studied, 3.1% developed CIN after the procedure. Among them 6.3% of CIN patients had anemia and the incidence in non anemic patients was 2.2% with the p value of <0.01[99].

In our study, the percentage of patients according to WHO criteria is 84.3%.The contribution of anemia as a risk factor for CIN is found to be 28.4% with a p value of 0.112 which is statiscally not significant.

RESULTS

With the variables-Age, Gendor, Smoking, DM, HT, ACE I and diuretics usage, NSAIDS and Nephrotoxic antibiotics usage ,as the risk factors for the development of contrast induced nephropathy,the significant contributing factor in our study is diabetic mellitus with totally 35 patients out of 102 ,in whom the incidence of CIN is 12 with the percentage of 34.3%.

Our study included only a small number of patients (n=102).When the number of patients are high in number, the yield of the result could be better. Also a long term follow up of the patients is needed.

CONCLUSIONS

From the 102 patients who underwent contrast using procedure-coronary angiogram over a period of three months, we concluded the following,

1. The incidence of CIN is 22.5%out of the 102 patients studied.
2. The contributing risk factors to CIN studied were age and gendor of the patients, HT, DM, use of nephrotoxic drugs namely ACE inhibitors, NSAIDS, diuretics, nephrotoxic antibiotics.
3. The significant contributing factor that contributed to CIN in our study is Diabetus mellitus with a p value of 0.049.
4. The mean s.creatinine value in CIN patients in our study is 1.77

	N	Minimum	Maximum	Mean	Std. Deviation
Age	102	18	78	52.53	10.174
Hb	102	9.0	16.0	11.729	1.0652
vol CM	102	30.0	50.0	42.696	6.8097
Creat – Baseline	102	.1	1.2	.789	.1711
Creat- post angio	102	.6	2.4	.881	.2864
CIN	102	1.0	2.4	1.775	.4200
Valid N (listwise)	102				

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SUMMARY

CIN is actually an iatrogenic form of disease. It is found in patients who are at risk and has an adverse outcome. There are many studies about CIN, but the definition and the inclusion criteria are not definite or conclusive. Careful selection of the patient ,decreasing the amount of contrast used by careful titering , proper periprocedural hydration have been found to decrease the incidence of CIN. [((oooo))]Also low or iso-osmolar contrast agents have lower renal injury when compared with high osmolar agents, hence they are found to have better safety profile.Drugs or medicines which are nephrotoxic should not be used for atleast 48 hours before the procedure. Hypotension should be corrected.Prophylactic hemofiltration should be done in very high risk individuals six hours before a complicated procedure, but guidelines or studies regarding it is available less. In patients who have already existing renal disease, hydration should be given 12 hours before the contrast using procedure and should be given for atleast 24 hours post procedure. Shorter interval between contrast procedures should always be avoided. Studies regarding N-acetyl cysteine is not complete, but the drug is cheaper, easy to administer and has decreased side effects. Its effects are better with higher doses.

In everyday clinical practice, the key role in patient protection from contrast-induced nephropathy is the proper monitoring of renal function, identification of patients with risk factors, and introduction of effective preventive measures. One of the most important components of comprehensive prophylaxis is close cooperation between the radiologist and the clinician referring the patient for contrast-enhanced procedures. The result of such cooperation is unquestionably a responsible referral of the patients for examinations and proper preparation of these patients, for example by development of a proper medical history questionnaire filled out before the examination, with involvement of the clinician, and allowing the radiologist to make conscious decisions and to plan the entire process before and after the examination.

MEDICAL HISTORY QUESTIONNAIRE

filled out by the physician referring the patient for an examination with the use of iodine contrast agents

1. Mild or severe reactions to iodine contrast agents	Yes*	No*
2. Allergic reactions requiring treatment	Yes	No
3. Bronchial asthma	Yes	No
4. Hyperthyroidism	Yes	No
5. Heart failure	Yes	No
6. Diabetes mellitus	Yes	No
7. Renal disease	Yes	No
8. Surgery on kidneys	Yes	No
9. Proteinuria	Yes	No
10. Hypertension	Yes	No
11. Gout	Yes	No

12. The last measurement of GFR or creatinine level

    value .....

    date .....

13. Is the patient on the following medications?:

• Metformin	Yes	No
• Interleukin-2	Yes	No
• NSAID	Yes	No
• Aminoglycosides	Yes	No
• Beta blockers	Yes	No
• Loop diuretics	Yes	No

Date of history taking

Signature
Stamp of the physician

*Circle the right answer

SCOPE FOR FUTURE STUDIES

The study done dealt with only some of the contributing factors for the occurrence of CIN. Furthur studies in the future should be concentrated on the prevention of CIN and prophylactic measures taken for the prevention of CIN.We have not included patients who are undergoing emergency angiographic procedure .There the risk factors are likely to be more and unique. Also such a setting will help in delineating the risk factors better.The possibility of further deterioration in renal function and permanent damage to renal function can be made out only if we do long term follow up of the patients who are developing CIN.

.

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INSTITUTIONAL ETHICAL COMMITTEE, STANLEY MEDICAL COLLEGE, CHENNAI-1

Title of the Work : Incidence of contrast induced nephropathy in patients With normal renal function undergoing contrast imaging study – coronary angiogram

Principal Investigator : Dr.S. Vanitha

Designation : PG in M.D.(Gen.Med)

Department : Department of General Medicine
Government Stanley Medical College,
Chennai-10

The request for an approval from the Institutional Ethical Committee (IEC) was considered on the IEC meeting held on 08.04.2013 at the Council Hall, Stanley Medical College, Chennai-1 at 2PM

The members of the Committee, the secretary and the Chairman are pleased to approve the proposed work mentioned above, submitted by the principal investigator.

The Principal investigator and their team are directed to adhere to the guidelines given below:

1. You should inform the IEC in case of changes in study procedure, site investigator investigation or guide or any other changes.
2. You should not deviate from the area of the work for which you applied for ethical clearance.
3. You should inform the IEC immediately, in case of any adverse events or serious adverse reaction.
4. You should abide to the rules and regulation of the institution(s).
5. You should complete the work within the specified period and if any extension of time is required, you should apply for permission again and do the work.
6. You should submit the summary of the work to the ethical committee on completion of the work.

19/12/13

MEMBER SECRETARY,
IEC, SMC, CHENNAI

CONSENT FORM

1). I agree to participate in the study entitled 'THE INCIDENCE OF CONTRAST NEPHROPATHY IN PATIENTS UNDERGOING CONTRAST IMAGING STUDY-CORONARY ARTERY ANGIOGRAM WITH NORMAL RENAL FUNCTION

2). I confirm that I have been told about this study in my mother tongue and have had the opportunity to ask questions

3). I understand that my participation is voluntary and I may refuse to participate at any time without giving any reasons and without affecting my benefits.

4). I agree not to restrict the use of any data or results that arise from this study.

Name of the participant :

Sign / Thumb print :

Sign of the Investigator

PROFORMA

Name :

Age / Sex : Marital Status :

Educational Status : Occupation :

Address :

Contact No :

Clinical features:-

Facial puffiness
Generalised Edema
Urine frequency
Dysuria
Burning Micturation
Altered sensorium
Loss of consciousness
Pleural Effusion
Ascitis
Fever

Past History:-

SLE……(duration……;treatment……)
Diabetes Mellitus……(duration……treatment……..)
Hypertension……(duration …….;treatment……)
IHD……(duration……;treatment……)
Stroke……(duration……;treatment……)
Renal disease
Other Autoimmune Disease
Liver disease
Thyroid dysfunction
Other Significant Past History :

Personal History:

Diet - vegetarian / non-vegetarian /mixed / fruits / fast food
Bowel - normal / constipation / loose stools
Bladder - normal / polyuria / oliguria
Smoking
Alcohol:
Tobacco

Treatment History Any H/o NSAID drug or Nephrotoxic antibiotics intake

General Physical Examination

Pallor
Icterus
Cyanosis
Clubbing
Lymphadenopathy
Pedal oedema

Vitals:

Temperature (in F)
Pulse (/min)
BP (mm of Hg)
Pulse pressure (mm of Hg)
Respiratory Rate

Systemic Examination :

CVS :

RS:

PA:

CNS:

ECG:

X ray chest :

Investigations :

Hb :
TC :
DC:
ESR
Platelet :

Renal Parameters :

B.Urea,

S.Creatinine

URINE
Sugar :
Protein (qualitative) : + / ++ / +++
Albumin
Cells / Casts

Ultrasound Abdomen :

Sl. No	Name	Age	Gendor	Smoker	HT	DM	ACE 1	DIUR	NSAID	NEP AB	DeHy	Hb	vol CM	Creat -B	Creat- P	CIN
1	Kesaram	55	1	2	2	1	1	2	1	2	2	12	50	0.6	0.7	2
2	Bhasker	62	1	1	1	1	1	2	2	2	2	16	30	0.9	0.8	2
3	Ramaiah	59	1	2	2	2	2	2	1	2	2	14	30	0.9	0.9	2
4	Ilango	55	1	1	2	2	2	2	2	2	2	13	50	0.8	0.9	2
5	citibabu	60	1	2	2	2	2	2	2	2	1	12	30	0.8	0.6	2
6	Gnanasekaran	51	1	2	1	1	1	2	2	2	2	11.8	30	1	1.3	1
7	selvi	47	2	2	2	1	2	2	2	2	2	11	50	0.8	0.7	2
8	sathyavathy	48	2	2	2	2	2	2	1	2	2	11.9	30	0.6	0.6	2
9	ramasamy	40	1	1	1	2	2	1	2	2	2	12.5	50	0.6	0.6	2
10	Rajan	38	1	2	2	2	2	2	2	2	1	13	50	0.7	0.6	2
11	malliga	57	2	2	1	2	1	1	1	2	2	10.6	50	0.8	0.7	2
12	Gopikrishna	27	1	2	1	2	2	2	2	2	1	13	50	0.8	0.8	2
13	svasamithran	65	1	2	2	2	1	2	1	2	2	11	30	0.8	1	1
14	Ramachandran	65	1	2	2	2	2	2	2	2	2	12.3	30	0.8	0.8	2
15	Kovilpillai	45	1	1	1	2	1	2	2	2	2	10	50	0.6	0.6	2
16	prabha	50	2	2	2	1	1	2	1	2	2	11	40	0.7	0.8	2
17	Mayarathy	55	2	2	2	1	1	2	1	2	2	11	40	0.7	0.8	2
18	Susairaja	53	1	1	2	2	2	2	2	2	2	12	50	1	0.9	2
19	Malathy	55	2	2	1	1	1	1	1	2	2	10.6	50	1	0.9	2
20	Subbaiah	55	1	1	2	2	2	2	2	2	2	13	50	0.8	0.9	2
21	Manoj Thomas	52	1	2	2	2	2	2	2	2	2	13	50	0.7	0.7	2
22	Suresh	55	1	2	1	2	2	2	2	2	2	11.4	50	1	1.6	1
23	Lakshmi	42	2	2	2	1	2	2	1	2	2	11.6	50	0.8	0.8	2
24	Shanmugam	65	1	2	2	1	2	2	2	2	2	12	50	0.8	0.9	2
25	Gnananmbigai	35	2	2	2	1	1	2	2	2	2	12.5	50	0.5	0.6	2
26	Gajendran	49	1	1	1	2	2	1	2	2	2	13	40	1	1	2
27	Adilamilagai	55	1	1	1	2	2	2	2	1	2	10.2	40	0.5	1.2	1
28	Siva	72	1	2	2	2	2	2	2	2	1	11.7	50	1.1	1.1	2
29	**Marimuthu**	75	1	1	2	2	2	2	2	2	2	11.9	50	1.1	1.16	2
30	Srinivasa	45	1	2	1	1	1	2	1	2	2	12	50	0.8	1.2	1
31	Mohan	57	1	2	1	1	1	1	2	2	2	13.1	50	1.2	1	2
32	Asirvatham	66	1	2	2	2	2	2	1	2	2	12.8	50	0.8	0.8	2
33	Govindhan	47	1	2	2	2	2	2	2	2	2	11	40	1	1.1	2
34	Soundararaj	55	1	1	2	1	1	2	2	2	2	11.9	50	0.6	0.8	1
35	Mani	40	1	2	2	2	2	2	2	2	2	12	40	0.7	0.8	2
36	Puviyarasan	64	1	1	2	1	1	1	1	2	2	11.6	50	0.5	0.9	1
37	Loganathan	45	1	2	1	2	2	2	2	2	2	12.5	30	0.6	0.7	2
38	Ramachandran	64	1	2	2	2	2	2	1	2	2	11.2	30	0.7	0.6	2
39	Iniyan	46	1	1	2	2	2	2	2	2	2	11.2	50	0.8	1	1
40	Rajan	52	1	2	2	2	2	2	2	2	2	11	50	0.9	2.4	1
41	Bhaskar	64	1	2	1	1	1	1	2	2	2	12	50	0.9	0.8	2
42	Periyasamy	47	1	1	2	2	2	2	2	2	2	14	50	0.5	0.9	1
43	Harikrishna	65	1	2	2	2	2	2	2	2	2	12.8	50	0.8	0.9	2
44	Malar	18	2	2	2	2	2	2	2	2	1	12.5	30	0.6	0.7	2
45	munusamy	45	1	1	2	1	1	1	2	2	2	12.4	50	0.6	0.6	2
46	Anwar basha	55	1	1	1	2	2	2	1	2	2	11.5	30	0.8	1.3	1
47	Vincent	47	1	1	2	2	1	2	2	2	2	11.9	50	0.7	0.8	2
48	thangavelu	49	1	1	1	2	2	2	2	2	2	12.5	40	1	0.8	2
49	Pfizer basha	60	1	1	1	2	2	2	2	2	2	11.5	50	0.8	0.7	2
50	Vijaya	60	2	2	2	1	1	2	1	2	2	10	50	0.6	0.7	2
51	Anandhavelu	35	1	1	2	2	2	2	2	2	2	13	50	0.7	0.6	2
52	Girija	40	2	2	2	1	1	2	2	2	2	12	40	0.8	0.7	2
53	Anand Kumar	40	1	1	2	2	2	2	2	2	2	12.9	50	0.1	0.7	2
54	Shahid	37	1	1	2	1	1	2	2	2	2	11.9	50	0.8	0.8	2
55	Rajamary	64	2	2	1	2	2	2	2	2	2	11.4	50	0.7	0.7	2
56	Kalaiarasan	50	1	2	2	1	2	2	2	2	2	12.8	50	0.8	1	1
57	Guna sekaran	53	1	2	1	1	1	2	2	2	2	11	30	0.8	1.5	1
58	Muhamed	60	1	1	2	1	2	1	1	1	1	11	50	0.7	1.1	1
59	Velu	59	1	2	2	2	2	2	2	2	2	10.9	50	1.1	1.1	2
60	Muthu	70	1	2	2	2	2	2	2	2	1	11.6	50	0.8	1.1	1
61	Veerabathran	45	1	1	1	2	1	1	2	2	2	12	30	0.6	0.7	2
62	Yugamoorthi	42	1	2	2	1	2	2	2	2	2	12.2	40	0.7	1	1
63	murugesan	42	1	2	2	2	2	2	2	2	2	11.9	40	0.8	1	1
64	Manivel	44	1	2	2	2	2	2	2	2	2	12	30	0.9	1	2
65	Gunasekaran	40	1	1	2	1	2	2	2	2	2	12.8	30	0.5	0.8	1
66	Hussain	57	1	2	1	2	2	2	2	1	2	12.9	50	1	0.8	2
67	Bharani	52	2	2	1	1	1	2	2	2	2	9.8	50	0.8	0.9	2
68	Peethambaram	50	1	1	1	2	1	2	2	2	2	12.2	30	0.7	1	1
69	subbaiya	60	1	2	2	2	2	2	2	2	1	13.2	50	0.7	0.7	2
70	annappan	66	1	1	2	1	2	2	2	2	2	11.2	50	0.6	0.7	2
71	Kasi	55	1	2	2	2	2	2	2	2	2	12	50	1	0.9	2
72	Elangoram	45	1	1	2	2	2	2	2	2	2	11.8	50	0.8	0.9	2
73	Mariamma	48	2	2	2	1	1	2	2	2	2	10.1	40	0.7	1.1	1
74	Padmini	50	2	2	2	2	2	2	1	2	2	11.4	50	0.8	0.8	2
75	Velu	45	1	2	2	2	2	2	2	2	2	9.6	50	0.9	0.7	2
76	Selvaraj	55	1	1	2	2	2	2	2	2	2	11.8	40	0.8	1.2	1
77	kanchana	61	2	2	1	1	2	2	2	2	2	10.4	40	0.8	1	1
78	Noorayisha	78	2	2	2	1	1	1	2	2	1	10.3	50	1.1	2.3	1
79	Gunasundari	45	2	2	1	2	1	1	1	2	2	10	50	1.1	0.8	2
80	Ayyayasamy	62	1	1	1	2	1	2	2	2	2	11.8	50	0.7	0.6	2
81	Muthumani	45	1	1	2	1	1	2	2	2	2	12	50	0.9	1	2
82	Umapathy	52	1	1	2	2	2	2	1	2	2	12	50	0.9	0.8	2
83	Ranjan	57	1	1	1	2	2	2	1	2	2	10.6	40	0.8	0.7	2
84	Mohanraj	32	1	1	2	2	2	2	1	2	2	10.4	40	0.7	0.8	2
85	Malliga	52	2	2	1	2	2	2	1	2	2	10.6	50	0.9	0.7	2
86	Krishnan	65	1	1	1	1	1	1	2	2	2	12.7	50	0.7	0.8	2
87	Ganapathy	65	1	2	1	1	1	2	1	2	2	9	50	1	1.1	2
88	Rambai	52	2	2	1	2	2	2	2	2	2	11.8	40	0.7	0.7	2
89	Adhilakhsmi	52	2	2	1	2	1	2	2	2	2	12.5	50	0.7	0.6	2
90	Srikumar	40	1	2	2	1	2	2	2	2	2	1.4	50	0.8	0.85	2
91	Kenneith	65	1	2	1	2	2	2	2	2	2	11.4	50	1	0.9	2
92	Durai	50	1	1	2	2	2	2	2	2	2	11.2	50	1.1	0.7	2
93	Soundarraj	55	1	2	2	2	2	2	2	2	1	11	50	1	0.7	2
94	Kumar	55	1	1	1	1	1	2	2	2	2	11	50	0.7	0.8	2
95	Fousea	50	2	2	1	2	2	2	1	2	2	10.8	50	0.9	0.7	2
96	Durai	45	1	1	2	2	2	2	2	2	2	11.9	50	0.9	0.8	2
97	Govindan	57	1	2	2	2	2	2	2	2	2	12.9	50	0.7	0.8	2
98	Peerson	53	1	2	2	2	2	2	1	1	2	11	40	0.6	0.6	2
99	Amritha	65	2	2	2	1	2	2	1	2	2	11.6	50	0.9	0.8	2
100	Harikrishnan	65	1	2	2	2	2	2	1	2	1	10	50	0.8	0.8	2
101	velmurugan	54	1	1	2	2	2	2	2	2	2	11	50	0.6	0.7	2
102	palanisamy	49	1	2	2	2	2	2	2	2	2	12.3	50	0.8	0.9	2

1 - Yes
2 - No

NSAID - Non Steroidal Anti Inflammatory Drugs
NEP AB - Nephrotoxic Antibiotics

Creat- B - Serum Creatinine Before the procedure
Creat- p - Serum Creatinine post procedure

DM - Diabtes Mellitus
HT - Hypertension

ACE I - Angiotensin Converting Enzymne Inhibitor
DeHy - Dehydration

Hb - Hemoglobin
CIN - Contrast Induced Nephropathy

Sl. No	Name	Age	Gendor	Smoker	HT	DM	ACE I	DIUR	NSAID	NEP AB	DeHy	Hb	Vol CM	Creat -B	Creat- P	CIN